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1. Rothman, J. and Shapiro, A. L.: Med. Clin. N. Amer. 33:274-5, Jan., 1949.
2. Stieglitz, E. J.: Geriatric Medicine, p. 848, 1943.

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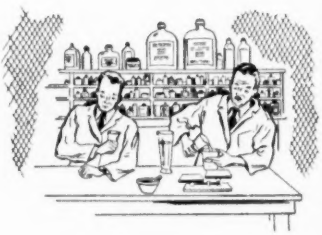

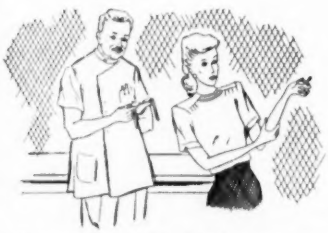

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2 Perrin, Samuel R.: Clinical Safety of Polysorb, Postgraduate Med. 8:485 (Dec.) 1950.

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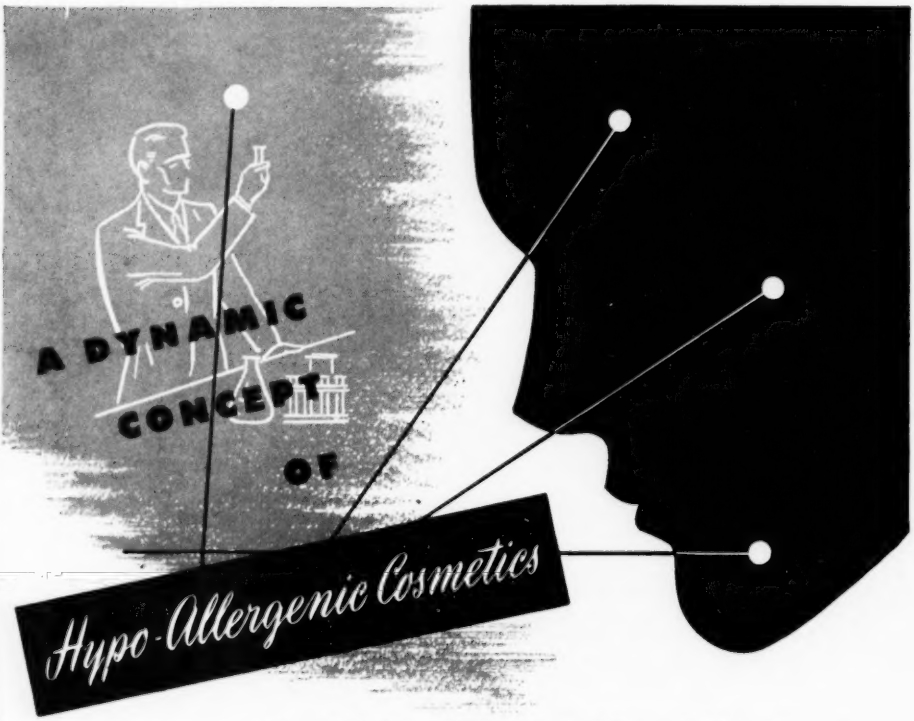

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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

6 Pascher, Frances, M.D.; Sawicky, H. H., M.D.; Silverberg, M.G., M.D.; and Emmet, Richard, M.D.; Bistrimate for Lupus Erythematosus, Lichen Planus and other Dermatoses. Journal of Investigative Dermatology, vol. 10, #6, June 1948.

7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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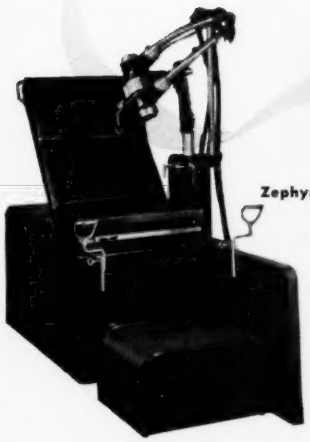

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HUMAN MELANOGENESIS

The Tyrosinase Reaction in Pigment Cell Neoplasms, with Particular Reference to the Malignant Melanoma: Preliminary Report

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ONE OF the major objectives in the study of the biochemistry of cancer is to establish a difference in the nature or quantity of enzymes present in normal and in malignant tissues. If it could be shown that a malignant tumor contained an enzyme not present in a benign tumor of the same type or in normal tissue of the cell type from which the tumor was derived, then it might be possible to inhibit selectively the enzyme peculiar to the tumor and consequently impair the growth of the tumor without affecting the metabolism of the normal cells. Furthermore, if it could be demonstrated that the activity of an enzyme in normal cells differed from that in malignant cells, the pathogenesis of the change from a benign to a malignant state might become apparent. In the past few years investigation of the enzyme systems of normal and malignant melanogenocytes [1] has revealed that the state of the tyrosine-tyrosinase system in normal cells may be different from that in malignant cells. The following facts have been established:

1. The enzyme, tyrosinase, which previously was shown to be present in plants, marine animals, and insects, has been demonstrated in mammalian tissues,[2] includ-

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Read at the meeting of the American Dermatological Association, Hot Springs, Va., May 23, 1951. This article won first prize in First Annual Prize Essay Contest of the Association.

Dr. S. William Becker, Jr., Fellow in Dermatology and Syphilology, Mayo Foundation, gave assistance in part of this work, and Dr. Hamilton Montgomery and Dr. A. Bunson Lerner gave their assistance and advice in this study.

Abridgment of a portion of a thesis submitted by Dr. Fitzpatrick to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Dermatology and Syphilology.

1. Since this paper was read, the term melanogenocyte has been suggested as a more suitable designation for mature melanin-forming cells than the presently used term melanoblast (Becker, S. W., Jr.; Fitzpatrick, T. B., and Montgomery, H.: Human Melanogenesis: Cytology and Histology of Pigment Cells [Melanodendrocytes], A. M. A. Arch. Dermat. & Syph., to be published. Fitzpatrick, T. B., and Lerner, A. B.: Melanin Pigmentation, in Wohl, M. G.: Internal Medicine, Ed. 5, Philadelphia, Lea & Febiger, 1951).

2. (*a*) Fitzpatrick, T. B.; Lerner, A. B.; Calkins, E., and Summerson, W. H.: The Occurrence of Tyrosinase in Horse and Fish Melanomas, Proc. Soc. Exper. Biol. & Med. **75**:395-398 (Nov.) 1950. (*b*) Lerner, A. B.; Fitzpatrick, T. B.; Calkins, E., and Summerson, W. H.: Mammalian Tyrosinase: Preparation and Properties, J. Biol. Chem. **178**:185-195 (March) 1949.

ing human skin.[3] This enzyme requires copper [4] for activity and is attached to cytoplasmic inclusions called mitochondria.[5] Under certain experimental conditions the original distinction between tyrosinase and dopa-oxidase is no longer valid, and both activities can be accounted for by a single enzyme.[2b]

2. Tyrosine, a stable amino acid, is most probably the physiological precursor of melanin in mammals, including man.[3] Tyrosine is the major and initial substrate of the enzyme tyrosinase.[2b]

3. In the presence of molecular oxygen, the enzyme, tyrosinase, catalyzes the oxidation of the colorless amino acid, tyrosine, to melanin, an insoluble polymer of high molecular weight. This enzymatic reaction is controlled by several physicochemical factors including oxidation-reduction potentials and naturally occurring sulfhydryl compounds in the epidermis.[6] The sulfhydryl groups may be important in binding copper, which is required for tyrosinase activity, and thereby inhibiting the enzyme action.

4. Radiant energy (ultraviolet rays, thorium-X, and x-rays) has been shown to "activate" the melanogenocytes of human skin.[3] These cells are able to form melanin when irradiated human skin slices are incubated with tyrosine. The tyrosinase in normal unirradiated melanogenocytes is unable to combine with tyrosine to form melanin in vitro.

In the biochemical and histochemical studies with human tissue cited later in this paper, the tyrosine-tyrosinase system is shown to exist in an inhibited state in unirradiated normal melanogenocytes, pigmented nevi, ephelides, lentigines, and verrucae seniles. In irradiated normal melanogenocytes and in malignant melanoma cells, the tyrosine-tyrosinase system is shown to be present in an active state. The terms "inhibited" and "active" refer therefore to the ability of the tyrosinase system within the pigment cell to convert the substrate tyrosine to melanin. The association of the activation of the tyrosinase system with the development of malignancy in the melanogenocyte and the use of the histochemical tyrosinase reaction for the identification of amelanotic melanomas will be discussed.

EXPERIMENTS AND RESULTS

Histochemical Studies.—To demonstrate tyrosinase histochemically, 1- to 3-mm. slices of tissue were fixed in 10% formalin for one hour, then incubated in 0.005-molar l-tyrosine in 0.1-molar phosphate buffer at pH 6.8 in the cold (0 to 4 C.) for 24 hours, and then kept in tyrosine at 37 C. for 24 hours. Control slices were incubated with phosphate buffer without added tyrosine. To prepare the tissue for histological examination, further fixation was carried out

3. Fitzpatrick, T. B.; Becker, S. W., Jr.; Lerner, A. B., and Montgomery, H.: Tyrosinase in Human Skin: Demonstration of Its Presence and Its Role in Human Melanin Formation, Science **112**:223-225 (Aug.) 1950.

4. Lerner, A. B.; Fitzpatrick, T. B.; Calkins, E., and Summerson, W. H.: Mammalian Tyrosinase: The Relationship of Copper to Enzymatic Activity, J. Biol. Chem. **187**:793-802 (Dec.) 1950.

5. Dubuy, H. G.; Woods, M. W.; Burk, D., and Lackey, M. D.: Enzymatic Activities of Isolated Amelanotic and Melanotic Granules of Mouse Melanomas and a Suggested Relationship to Mitochondria, J. Nat. Cancer Inst. **9**:325-336 (Feb.) 1949.

6. Lerner, A. B., and Fitzpatrick, T. B.: Biochemistry of Melanin Formation, Physiol. Rev. **30**:91-126 (Jan.) 1950.

by immersing the tissue slices in formalin for 24 hours, after which they were dehydrated, cleared in toluene, imbedded in paraffin, and sectioned at 15 μ, in most instances.

In the case of the amelanotic melanoma, frozen sections cut at 8 μ were made from the fixed tissue slices, since it was found that some of the melanin which had been formed by incubation with tyrosine was lost when paraffin sections were made.

Normal Human Tissues: Slices of material from surgical and unembalmed necropsy specimens were tested to determine the presence of tyrosinase. Sections or slices of normal human liver, kidney, brain, adrenal, bone marrow, melanogenocytes in the leptomeninges, and fresh unfixed blood films all showed a negative tyrosinase reaction. In the case of the blood films, dopa (dihydroxyphenylalanine) was oxidized by the granules of the polymorphonuclear neutrophils to melanin, but tyrosine was not. The oxidation of dopa by these granules was probably due to the presence of oxidases or peroxidases other than tyrosinase. The oxidation of dopa by the oxidases of the leucocytes emphasizes the nonspecific nature of dopa oxidation by human tissues, whereas the oxidation of tyrosine to melanin requires specific enzymatic (tyrosinase) activity.

Tissue slices of human white skin failed to show evidence of tyrosinase activity in the melanogenocytes.

Irradiation of Normal Human Skin (in Vivo) with Ultraviolet Radiant Energy: Nonpigmented blond skin from 30 normal human volunteers was irradiated daily for five to eight days with erythema doses of ultraviolet radiant energy obtained from a quartz-mercury vapor lamp. Figure 1*a* illustrates the melanogenocytes lying deep in the basal-cell layer at the epidermal-dermal junction. The control section (Fig. 1*b*) and portions of unirradiated skin from the same donor also incubated in tyrosine failed to show the presence of melanogenocytes.

Irradiation of Normal Human Skin (in Vitro) with Ultraviolet Radiant Energy: Normal human skin was irradiated daily on the epidermal side with erythema doses of ultraviolet radiant energy for five days. During the intervals between irradiation, the skin was stored in the cold to preserve the enzyme activity. The tyrosinase reaction in the irradiated skin was invariably negative.

Effect of Sulfhydryl Inhibitors on Activation of Tyrosinase Reaction: Sodium arsenite and iodoacetamide were incubated separately with normal human skin prior to and during incubation with tyrosine. These agents failed to remove the inhibition of tyrosinase which occurs in normal skin.

Effect of Small Amount of Dopa on Tyrosinase Reaction in Normal Skin: Mixtures of tyrosine and dopa in a ratio of 10 to 1 did not result in appreciable tyrosinase activity in the melanogenocytes, although there were more visible melanogenocytes in the slices incubated in the tyrosine-dopa mixtures than in the buffer controls.

Tyrosinase Reaction in Pigmented Nevi: Twelve dermal and junctional nevi showed a negative or weakly positive tyrosinase reaction. A definitely darker color of actively proliferating junctional-type nevi can be detected grossly in the slices of nevi incubated in tyrosine. This difference in color is not discernible in the histological sections. Figure 2 illustrates a dermal nevus containing clumps of typical nevus cells but exhibiting a negative tyrosinase reaction. As will be

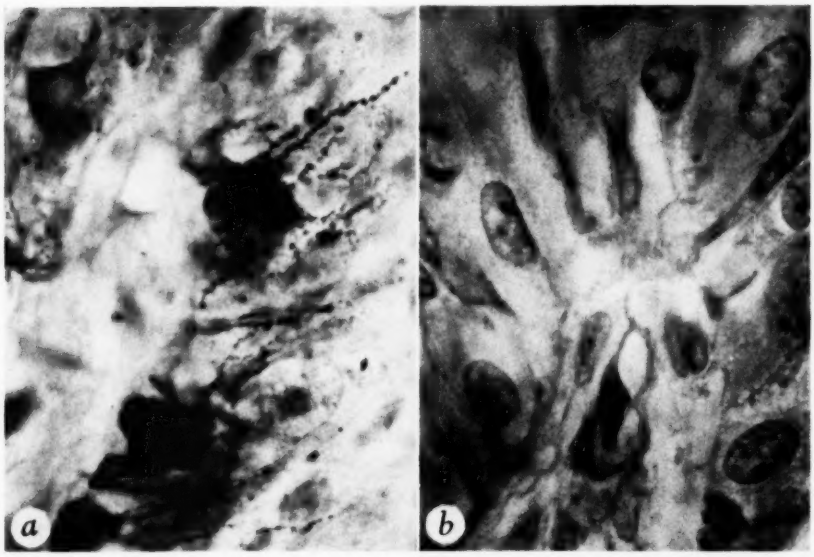

Fig. 1.—Tyrosinase reaction in irradiated and unirradiated normal skin. (*a*) Melanogenocytes in human skin exposed in vivo to ultraviolet radiant energy and incubated in tyrosine phosphate buffer. These cells contain an active tyrosinase system. Slices of irradiated skin incubated in phosphate buffer without added tyrosine showed complete absence of pigment in the melanogenocytes similar to those in *b;* paraffin sections; × 1,025. (*b*) Slices of unirradiated portion of skin, same donor as *a,* which have been incubated in tyrosine phosphate buffer under the same conditions in *a.* Note complete absence of pigment. These melanogenocytes contain an inhibited tyrosinase system; paraffin sections; × 1,025.

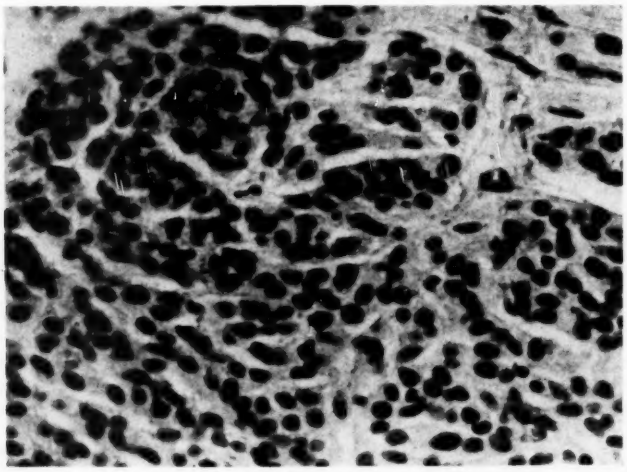

Fig. 2.—Dermal nevus; slices of dermal nevus tissue incubated in tyrosine phosphate buffer under the same conditions as in Figure 1*a.* Note complete absence of pigment in the nevus cells. These cells contain an inhibited tyrosinase system. It is possible to activate the tyrosinase in the nevus cells near the epidermal-dermal junction by ultraviolet radiant energy, but reaction is weak because of lack of penetration of the ultraviolet radiant energy; × 425.

discussed later in this paper, the tyrosinase histochemical reaction cannot be carried out in nevi containing appreciable quantities of preformed melanin because new melanin formation cannot be estimated.

Tyrosinase Reaction in Amelanotic Melanoma: Figure 3 illustrates the marked difference seen grossly in slices of amelanotic melanoma incubated in tyrosine and in buffer without added tyrosine. Figure 4 shows, with control sections for comparison, the presence of fine granules of melanin in the tumor cells. This melanin was produced in vitro by the reaction of the active tyrosinase system within the tumor cells and the substrate tyrosine in which the tumor slices were incubated. This reaction resulted in the formation of insoluble melanin which was precipitated at the site of its formation as a brown pigment. In the control tumor slice incubated in phosphate buffer without added tyrosine, the cells were com-

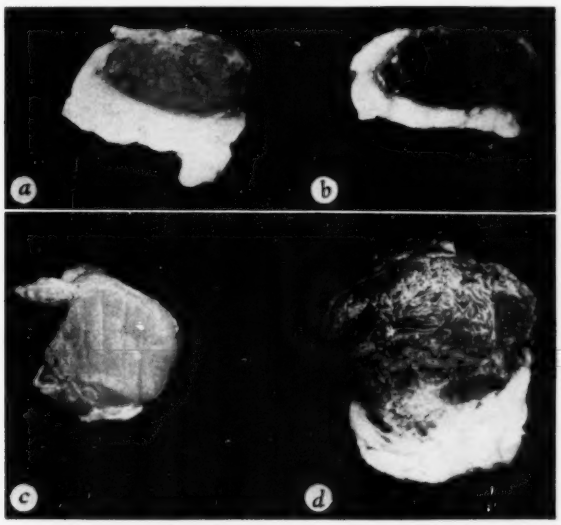

Fig. 3.—Amelanotic malignant melanoma: (*a* and *b*) woman, aged 63; (*c* and *d*) man, aged 52. Amelanotic malignant melanoma nodules were divided into two slices. Slices *a* and *c* were incubated in phosphate buffer without added tyrosine and retained the same pale color as before. Slices *b* and *d* were incubated in tyrosine phosphate buffer and turned black because of the deposition of melanin formed by interaction of substrate tyrosine with the active tyrosinase system contained in the malignant cells.

pletely devoid of melanin. From histological examination alone, it is not possible to identify this lesion as a melanoma, since a grade-4 (Broders' method) fibrosarcoma or squamous-cell carcinoma or other highly undifferentiated tumor could give the same histological picture. These findings were duplicated in six additional human amelanotic melanomas.

Tyrosinase Reaction in Other Neoplasms: Slices of carcinoma of the breast, embryoma of the kidney, bronchogenic carcinoma of the lung, lymphosarcoma, squamous-cell carcinoma, pigmented basal-cell epithelioma, verruca senilis, lentigo, and ephelides all failed to give the tyrosinase reaction.

Biochemical Studies.—Tyrosinase activity in the preparations discussed later was determined manometrically by measurement of oxygen uptake in the Warburg

apparatus at 38 C. with 0.1-molar potassium phosphate buffer at pH 6.8. The substrate, tyrosine, was added from the side arm to the enzyme preparations after 10 minutes' equilibration at 38 C.

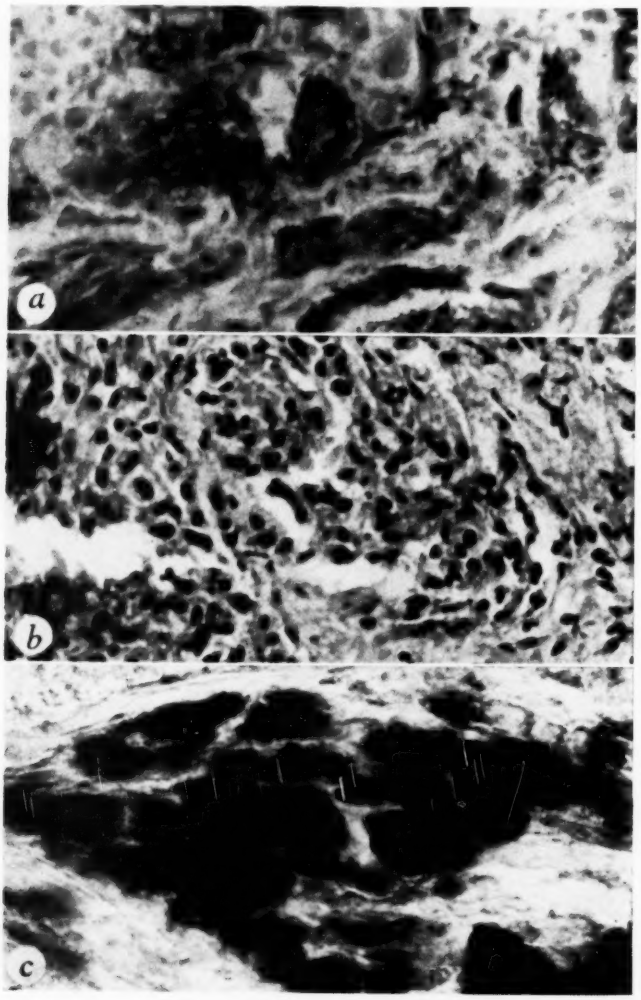

Fig. 4.—Amelanotic malignant melanoma. (*a*) Incubated in tyrosine; intensely pigmented malignant-melanoma cells from tumor nodule *b* in Figure 3. Melanin is deposited in the form of fine, densely packed brown granules; frozen sections; × 425. (*b*) Incubated in phosphate buffer without added tyrosine; malignant-melanoma cells from tumor nodule *a* in Figure 3, showing complete absence of melanin; frozen sections; × 425. (*c*) Higher magnification of tumor cells from tumor nodule *b* in Figure 3. The nucleus has been obscured by melanin deposits, but serial sections show that melanin is deposited only in cytoplasm since the enzyme tyrosinase is attached to cytoplasmic particles called mitochondria (Dubuy, H. G., and others: J. Nat. Cancer Inst. **9**:325-336 [Feb.] 1949; frozen sections; × 825.

Tyrosinase Activity in Normal Human Skin: Many types of preparations of normal human white and Negro skin were tested for tyrosinase activity. These included whole skin (epidermis and dermis), epidermal sheets separated from the dermis by enzymatic digestion in pancreatin, skin slices, homogenates of whole skin, and homogenates of separated epidermis. Also included were extracts obtained from skin powder which had been prepared by freezing skin in liquid air and forcing it through a cold Wiley mill kept constantly in the deep freeze, according to a technique developed by Lerner.[7] All preparations showed complete absence of tyrosinase activity, as measured according to the conditions outlined. Unfortunately, it was not possible to obtain sufficient quantities of human skin which had been irradiated in vivo. It appears likely that tyrosinase activity could be demonstrated in extracts of irradiated skin, since tyrosinase activity was invariably present in irradiated skin, as demonstrated previously with histochemical studies.

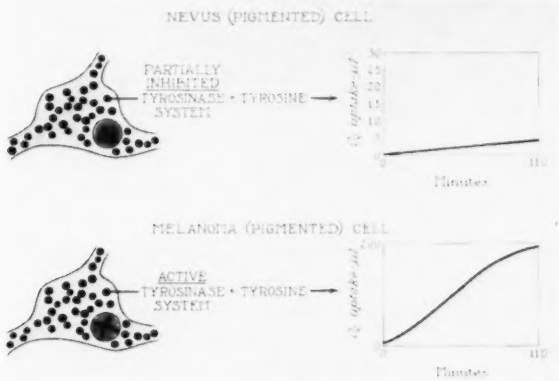

Fig. 5.—Oxygen consumption of benign malignant pigment-cell neoplasms on addition of tyrosine, comparable amounts of tissue being used.

Because inhibitory sulfhydryl groups are present in normal skin[8] and these groups are decreased after irradiation[9] with ultraviolet radiant energy, several types of sulfhydryl inhibitors were tried with the various types of preparations of normal unirradiated skin. These agents included adequate concentrations of *p*-chloromercuribenzoic acid and iodoacetamide. There was no evidence of tyrosinase activity in the presence of the sulfhydryl inhibitor. Small amounts of dopa, previously shown[2b] to catalyze the enzymatic oxidation of tyrosine, were added to the various tyrosine-extract mixtures; but there was no evidence of tyrosine oxidation.

Tyrosinase Activity in Pigmented Nevi: Actively proliferating junctional-type nevi show a slow but definite oxygen uptake with tyrosine as the substrate, as

7. Lerner, A. B.: Preparation of Skin Powder and Skin Extracts, J. Invest. Dermat. **17**:251-254 (Oct.) 1951.

8. Rothman, S.; Krysa, H. F., and Smiljanic, A. M.: Inhibitory Action of Human Epidermis on Melanin Formation, Proc. Soc. Exper. Biol. & Med. **62**:208-209 (June) 1946.

9. Flesch, P., and Rothman, S.: Role of Sulfhydryl Compounds in Pigmentation, Science **108**:505-506 (Nov.) 1948.

illustrated in Figure 5. Dermal nevi show an insignificant oxygen uptake after the addition of tyrosine.

Tyrosinase Activity in Human Malignant Melanomas: In contrast to the completely negative results with unirradiated normal human skin, both melanotic and amelanotic melanoma extracts or tissue slices were found to contain significant tyrosinase activity (Fig. 5). The extracts were prepared by grinding 5 gm. of fresh tumor with sand and Ringer's solution for 10 minutes and centrifuging at 1,500 revolutions per minute for 5 minutes to remove the sand and cellular debris. This is similar to results demonstrating an active tyrosinase system in the mouse-,[2b] horse-,[2a] and fish-melanoma[2a] extracts. The amelanotic-extract-tyrosine mixture, which was light gray at the onset, turned jet black at the completion of the experiment. This is in agreement with the results obtained on the amelanotic melanoma by the histochemical studies cited previously. It is evident from Figure 5 that there is a difference in the rate and total amount of oxygen uptake in junctional nevi and malignant melanomas.

COMMENT

From the foregoing histochemical and biochemical studies it is possible to make the following statements regarding the tyrosine-tyrosinase reaction in human tissue:

1. An inhibited tyrosinase system occurs in unirradiated skin. A partially inhibited tyrosinase system appears to exist in actively proliferating junctional nevi.

2. An active tyrosinase system occurs in melanotic and amelanotic melanomas and in human skin irradiated with ultraviolet radiant energy.

3. Other neoplasms (benign and malignant) do not contain tyrosinase activity.

These findings are illustrated diagrammatically in Figures 6 and 7.

The mechanism by which ultraviolet radiant energy activates the human tyrosinase system is unknown. In a recent publication[10] two possible explanations were offered. First, trace amounts of dopa, which are known to accelerate greatly the tyrosine-tyrosinase reaction, may be formed in the melanogenocyte or surrounding cells. Dopa formed by direct photochemical oxidation of tyrosine present in the tissues may then catalyze the enzymatic oxidation of tyrosine to melanin. The histochemical and biochemical studies do not support this hypothesis as the sole explanation for the activation of the tyrosinase system, since addition of small amounts of dopa showed only a slight and insignificant increase in tyrosine oxidation by normal skin. Second, ultraviolet radiant energy may decrease the concentration of normally occurring sulfhydryl groups in the epidermis. This view also does not appear to be the sole explanation of the activation process, since several powerful sulfhydryl inhibitors failed to promote the oxidation of tyrosine by normal-human-skin preparations, or to produce a positive histochemical tyrosinase reaction.

A comparative biochemical study of tyrosinase throughout the plant and lower-animal kingdoms revealed the presence of an active tyrosinase system in most

10. Fitzpatrick, T. B.; Lerner, A. B.; Calkins, E., and Summerson, W. H.: Mammalian Tyrosinase: Melanin Formation by Ultraviolet Irradiation, Arch. Dermat. & Syph. **59**:620-625 (June) 1949.

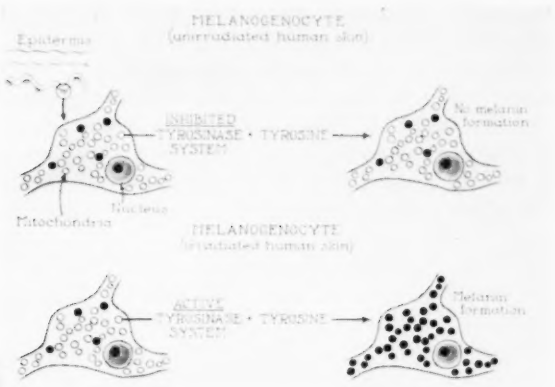

Fig. 6.—Tyrosine-tyrosinase systems in normal unirradiated and ultraviolet-irradiated human skin.

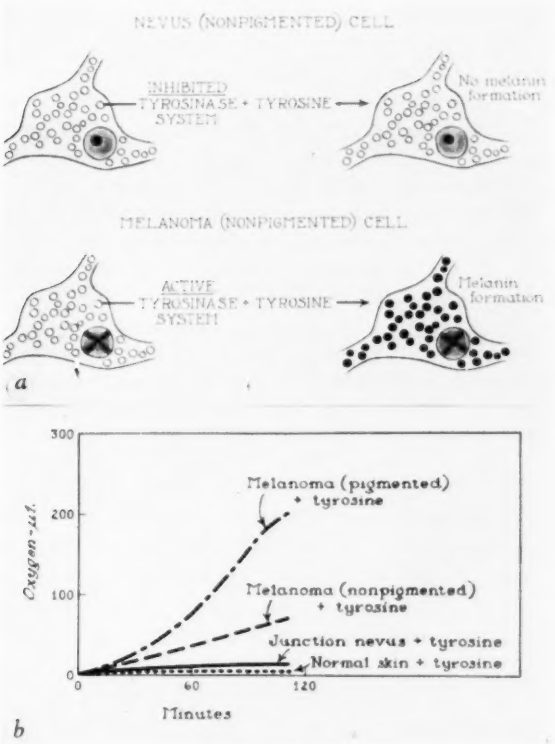

Fig. 7.—(*a*) Tyrosine-tyrosinase systems in dermal (nonpigmented) nevi and amelanotic melanoma. (*b*) Comparison of oxygen consumption of junctional-type pigmented nevi and malignant melanoma.

plants,[6] marine animals,[2a] hemolymph of butterflies,[11] and feather germ of chicks,[12] and the presence of an inhibited tyrosinase system in the normal skin of mammals. It is possible that as we ascend phylogenetically from plants to man a control is placed over the activity of tyrosinase, and the enzyme is active only during periods of physiological production of melanin, and only when the melanogenocytes are exposed to activating factors, such as radiant energy, hormones, and so forth. This controlled rate of activity is lost when the pigment cell becomes malignant. In this situation melanin production is limited only by the availability of the substrate.

From the experimental results so far obtained, it appears that an active tyrosinase system is associated with the malignant character of the human pigment cell. The difference in the tyrosinase system in normal white human skin and malignant melanomas is, we believe, well established by these experiments. The absolute quantitative difference of tyrosinase activity of junctional-type nevi and malignant melanoma is not yet conclusively established, however, since it is difficult to obtain large quantities of nevus cells to carry out studies of oxygen consumption. In order to estimate tyrosinase activity accurately in small quantities of nevus tissue, microrespiration experiments are now being done. The histochemical tyrosinase reactions, which were studied in nevi containing relatively small amounts of pigment so that adequate comparisons could be made, indicated, however, the absence of an active tyrosinase system.

Since the preformed melanin in the normal melanogenocytes, nevus cells, or pigmented malignant-melanoma cells renders difficult the evaluation of histochemical studies based on new melanin formed in the cell, a method is being developed using tyrosine labeled with radioactive C^{14} as the substrate. The radioactive melanin formed in the reaction will be determined from radioautographs. The areas containing an active tyrosinase system will therefore be readily outlined with this technique. This technique could be used even in heavily pigmented lesions. The use of the radioautographic detection of an active tyrosinase system in pigmented tumors may prove to be a valuable method for judging the benign or malignant character of a given pigmented lesion. Furthermore, this technique may show the actual transition of a junctional-type nevus into a malignant melanoma before this change can be judged by histological examination alone.

The radioautographic technique would require only a few microtome sections of the tumor.

Further investigation may clarify the mechanism of the activation of the tyrosinase system and the reasons why tyrosinase in the normal melanogenocyte is present in an inhibited state. The chemical identification of the naturally occurring inhibitory factor or factors in the normal human pigment cell and nevus cell may serve as a pattern for the development and localization of specific inhibitors of tyrosinase in the malignant-melanoma cell. As these inhibitory factors become clearer so will the likelihood increase of finding a rational chemotherapeutic approach to the treatment of one of the most devastating and sinister of malignant lesions.

11. Hasebroeck, K.: Die Dopaoxydase (Bloch), ein neues melanisierendes Ferment im Schmetterlingsorganismus, Biol. Zentralbl. **41**:367-373 (Aug.) 1921.

12. Charles, D. R., and Rowles, M. E.: Tyrosinase in Feather Germs, Proc. Soc. Exper. Biol. & Med. **43**:55-58 (Jan.) 1940.

From a practical point of view, the histochemical and biochemical reactions for the demonstration of an active tyrosinase system in pigment cells should prove of value in differentiating the amelanotic melanoma from many other undifferentiated malignant neoplasms (fibrosarcoma, squamous-cell carcinoma, adenocarcinoma, etc.) which have a histological picture often indistinguishable from that of amelanotic melanoma. Furthermore, the measurement of oxygen uptake on addition of tyrosine to a given extract or slice of a pigment-cell neoplasm may provide a biochemical means of diagnosing malignant melanoma in a suspected lesion.

SUMMARY

1. The tyrosinase reaction appears to be associated with the malignant character of human pigment cells (melanogenocytes). Of the malignant neoplasms, melanoma cells alone form melanin when incubated in tyrosine. The other malignant tumors tested did not contain tyrosinase activity.

2. Nonmalignant pigment cells in normal skin require activation of the tyrosinase system by a stimulating factor (for example, radiant energy) in order to form melanin when incubated in tyrosine.

3. The tyrosinase reaction therefore may provide a new approach to (*a*) the diagnosis of malignancy in pigment-cell neoplasms (for example, junctional nevi versus malignant melanoma), and (*b*) the differentiation of amelanotic malignant melanoma from other highly undifferentiated malignant lesions which it simulates, such as fibrosarcoma, lymphoma, and squamous-cell carcinoma.

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ABSTRACT OF DISCUSSION

DR. HERMAN SHARLIT, New York: Dr. Fitzpatrick has been an untiring investigator in the pigment field and will be credited along with his collaborators with having demonstrated that the tyrosin-tyrosinase mechanism plays a part in melanin production in the human, as has long been demonstrated for comparable mechanism in lower forms of life. Dr. Fitzpatrick, in his provocative presentation, offers a wealth of experimental data secured by following sound orthodox lines in both his histochemical and biochemical procedures, to reveal some of the conditions under which an activated, that is, a functioning, tyrosinase can be demonstrated in tissue substances which physiologically possess the function of melanogenesis; in this instance, in normal skin and melanotic tumors of the skin.

His monometric studies with melanotic and amelanotic melanomas, using a tyrosine substrate, are unquestionably significant. Whether that significance is applicable to the problem of cancer or melanogenesis or even both has yet to be determined. The demonstration of an activated tyrosinase in the amelanotic masses reveals the breadth of the problem in melanogenesis and the importance, apparently, of the nonenzymatic steps in physiologic melanin production.

It must now be accepted that an enzymatic step is operative in melanogenesis in the conversion of a colorless mother substance or substances into the brownish-black particulate matter that we call melanin. Since our concern is with physiologic melanin, and since, unfortunately, we have up to this moment no other means of identifying this melanin except by the use of the laboratory microscope, the microscope has become an indispensable tool in this field of study. For this reason the histochemical technique has been not only an essential one in the pigment problem but also a comforting one, for it involves the use of that tool that is the ultimate resort in the clarification of the thinking emanating from the use of other techniques.

Considering the pigment problem strictly from the viewpoint of clinical medicine, I should say that over the years the histochemical method served more and more to reveal the problems

in the field and to check on the hypotheses worked out with the biochemical methods, and that gradually investigators by the latter methods preempted the whole field.

The history of the phenomenon of postmortem pigmentation of skin illustrates what I mean by "biochemical preemption of the field." At the outset many held that this apparent evidence of increased pigmentation was an optical illusion, that is, that there were relatively more pigment granules because of the postmortem dehydration and shriveling of cells and tissues containing them. Then arose the question of pigment particles *de novo* versus old particles made larger and darker and thus visible. Then followed the era, from which we are now apparently emerging, of the dopa reaction which served biochemists, as they saw it, to elect *de novo* melanin formation as the problem in skin pigmentation and to designate the cells in the skin that possess the sole capacity to build pigment *de novo*. This served to set apart, and apparently beyond worthiness of consideration as part of the pigment problem, many histochemical procedures on skin sections involving the incubation of these sections in substrates wholly devoid of any substance which might act as a premelanin, procedures which produced pigment in great profusion in many cells of the epidermis beyond the elect sites. Ten years ago I presented before this association findings of this type achieved through the use of cytotoxic poisons.

I cannot at this time pursue these points any further. I hope I shall be forgiven for having taken this opportunity to point out a thing which I consider a serious deviation from what is wholesome in research. I refer to arbitrarily defining the limits of a problem, a problem that has as many facets as the one of pigmentation of skin, a problem in which the substance of our concern is dark particulate matter wherever in the skin it is found or is artfully produced.

Tyrosine has now nudged dopa a bit to the side of the center spotlight. The enzyme chemists have achieved a confirmation of their suspicions via the microscope, and our prize essayist has played a leading part in the demonstration. Dr. Fitzpatrick's report is a genuine contribution, forcefully and clearly presented. I want to congratulate him.

DR. STEPHEN ROTHMAN, Chicago: Fitzpatrick, Lerner, and their associates have demonstrated by histochemical methods that normal skin possesses tyrosinase activity after the skin has been exposed to ultraviolet irradiation. This finding represents a brilliant confirmation of the sulfhydryl-inhibition concept which was developed at the University of Chicago in 1946 (*Proc. Soc. Exper. Biol. & Med.* **62**:208, 1946) and amply evidenced later on (*Science* **108**:505, 1948). This concept implies that white persons, although their pigment-forming cells contain both enzyme and substrate, have a white skin because sulfhydryl compounds inhibit the action of the enzyme on the substrate. Ultraviolet irradiation knocks out the inhibitor whereby the enzyme becomes liberated, and therefore it can be demonstrated histochemically. The liberated enzyme may act freely on the substrate, and pigmentation results. This mechanism is operating not only in sun tan but in all instances of postinflammatory pigmentation, including heat, ionizing radiation, and natural disease processes. At present we are studying the problem of whether the greatly intensified postinflammatory hyperpigmentation in patients treated with corticotropin (ACTH) treatment is based on the same mechanism.

It has been known for a long time that melanomas contain free, uninhibited tyrosinase. However, Dr. Fitzpatrick knew how to utilize this fact and how to develop an ingenious diagnostic procedure based on the quantitative differences of amounts of free enzyme in benign and malignant tissues. I wish to express my admiration of this work.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I am sorry that neither Dr. Samuel Peck nor Dr. S. W. Becker Sr., are present because they in the past have held opposite views regarding melanogenesis, and I, along with Dr. Peck, have been opposed to Masson's concept of a neuroepithelial origin of the clear and dendritic cells, whereas Dr. Becker Sr., has supported this concept. It remained for Dr. Fitzpatrick and Dr. Becker Jr., working in my laboratory, to convince me that the basal cells of the epidermis do not form pigment and that only the so-called dendritic cells form melanin pigment. The clear cells of Masson (*cellules claires*) are equivalent to the pigment-forming dendritic cells and do not arise from the basal cells of the epidermis as I, with others, formerly maintained. I am, therefore, going to have to change what I have said in the book with Ormsby, "Diseases of the Skin," in regard to the histology and histogenesis of pigmentation. Masson has recently referred to the cell of Langer-

hans, which is seen best with gold preparations, as a dead cell (*Cancer* **4**:9-38 [Jan.] 1951). Dr. Becker Jr., however, has clearly shown that gold impregnations of the skin resulted in wrinkling of the epidermis, and consequently serial sections revealed that the so-called Langerhans cell is not high up in the epidermis but is actually a dendritic cell lying at the epidermal-dermal junction. Dr. Fitzpatrick has clearly shown that the cells of malignant melanomas possess a positive tyrosinase reaction. There remains, however, much to be learned about pigment formation and melanogenesis, including the failure at present to obtain a positive tyrosinase reaction in pigmented nevi (moles) or in blue nevi and how to account for the increased melanin pigmentation seen in pigmented basal-cell epithelioma and verruca senilis (seborrheic keratosis).

Dr. Thomas B. Fitzpatrick, Rochester, Minn.: I would like to thank the discussers for their kind remarks. Both Dr. Sharlit and Dr. Rothman have contributed generously to our knowledge of melanogenesis.

The best evidence for the role of an enzyme in human melanin formation is the existence of the albino. It is believed by geneticists that single genes control single biochemical reactions, and that this control is exercised through the control of enzyme synthesis. If human melanin formation occurred by any other method than enzymatically, we would expect it to occur in human albino skin.

Because of the significance of the experimental findings reported today in the diagnosis of melanomas by means of biochemical procedure, more than the usual number of experiments must be carried out before these facts can be accepted as established. Further studies are now in progress, and it is my sincere belief that the clear-cut differentiation of pigmented nevi and malignant melanomas with these biochemical techniques will be maintained.

STRESS STUDIES IN THE ECZEMA-ASTHMA-HAY-FEVER DIATHESIS

THOMAS H. STERNBERG, M.D.
AND
MURRAY C. ZIMMERMAN, M.D.
LOS ANGELES

IN A PREVIOUS paper [1] we reported the effects of an artificially applied stress situation on the "alarm reaction" response of persons with the skin component of the eczema-asthma-hay-fever complex (atopic dermatitis). While the number of patients studied was small, there were definite indications of an abnormal response, as measured by the eosinopenic index and changes in the lymphocyte-neutrophile ratio. Our results supported Selye's concept [2] that the allergic or atopic diathesis should be included in the so-called diseases of adaptation. This concept holds that these diseases may depend largely upon a derangement of the pituitary-adrenocortical response to stress, and, further, that as for "triggering" the alarm reaction, there is little or no difference between physical and psychic or emotional stress.

In this paper we are reporting a continuation of our previous studies. Both our control and experimental groups have been considerably expanded. The alarm-reaction response, as we have measured it, has proved a valuable method of study of the effects of stress in this disease, and it is therefore possible to attach more significance to our data.

MATERIALS AND METHODS

Testing Technique.—All subjects were instructed to fast from 11 p. m. of the preceding night to 12:15 p. m. of the test day. Blood specimens were taken from the ear lobe at 8 a. m. and 12:15 p. m. of the test day. Each specimen was chambered and counted immediately for the eosinophile leucocytes by the Thorn modification [3] of the Dunger technique, using Levy counting chambers, 0.2 mm. deep. A routine Neubauer-chamber white count and a stained-smear

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1. Sternberg, T. H.; Butler, P. G., and Zimmerman, M. C.: Pituitary-Adrenocortical Functioning in Patients with Atopic Dermatitis, J. Invest. Dermat. **16**:5, 1951.

2. Selye, H.: The Alarm Reaction and General Adaptation Syndrome, J. Clin. Endocrinol. **6**:117, 1947.

3. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal-Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormones, J. A. M. A. **137**:1005 (July 17) 1948.

differential count were also done. To minimize technical error, at least two pipettes and four chambers were counted and averaged for each count. For eosinophile counts in normal controls, when the count was very low, three or four pipettes and six or eight chambers were counted to minimize the errors inherent in the use of small numbers.

Testing Procedure.—Each subject was tested on three separate nonconsecutive days. On the "control day," the subject had blood taken at 8 a. m. and then read or relaxed until 12: 15 p. m. when the second count was taken. This control day was included to acclimatize the patient to any possible stress of the test procedure, as a check on the patient's normal variation in eosinophile count, and as a check on the technical accuracy of the investigative technique.

On the "epinephrine day," each subject was given epinephrine subcutaneously, 0.01 mg. per kilogram of body weight, immediately after the 8 a. m. blood specimen was taken. The subject was then allowed to read or relax until the 12: 15 specimen was taken.

Our stress situation consisted of one hour in a hot room at 100 to 115 degrees F. and 85 to 90% humidity, as previously used by Pincus and Elmadjian.[4] On this test day, each subject was placed in the hot room immediately after the 8 a. m. specimen was taken. Subjects were allowed water as desired while in this room, but all sat quietly without exertion. All perspired profusely and were unanimous in their comments as to the unpleasantness of the experience. After leaving the hot room, these patients were allowed to shower and dress, and then they rested quietly until the 12: 15 blood specimen was taken.

Because of the phenomenon of refractoriness of response to brief stress situations reported by Michael,[5] the epinephrine day and the hot-room day were always at least four days apart. The order of days was made random by chance selection in order to rule out any possible effect of patterning on the experiment.

The only other known selection factor is that 7 of the 22 controls refused to tolerate the hot room for a full hour. Each of these patients had a normal eosinopenic stress response. All the atopic patients remained for a full hour, although they complained equally of the discomfort. In most instances, atopic and control patients were given the hot-room stress together to be certain that the same stimulus was given each.

Case Material.—The 22 control subjects were selected on a basis of age comparable to the atopic ones. Each control was apparently healthy and denied any history of eczema, asthma, hay fever, hives, migraine headaches, epilepsy, or allergic manifestations of any nature. All controls were ambulatory. It is worthy of note that one person in this group had a history of transient hypertension associated with nervous stress. Since this had no apparent relation to an atopic diathesis, she was accepted and is one of the controls showing an aberrant response. The only other selection factor in the control group involved one person who was discovered upon the first blood count to have eosinophilia of 1,400 per cubic millimeter. Stool examination revealed an asymptomatic hookworm infection apparently contracted in the South Pacific in 1945. Testing on this patient was postponed in favor of treatment of the hookworm infestation, and he was eliminated from the control series.

Twenty-seven patients were selected on a basis of clinical signs and symptoms of atopic dermatitis. All patients had active dermatitis of at least three years' duration at the time of testing. Great care was taken to select only typical, classic cases of atopic dermatitis with unanimous diagnostic agreement of the entire dermatology staff. There were 23 men and 4 women. Their ages ranged from 19 to 44, the average for the group being 27.7. Twenty-one of the patients were hospitalized at the Veterans' Administration hospital; the others were our private patients. There was a history of eczema, asthma, hay fever, hives, or other allergic manifestations in siblings, parents, or children of 19 patients, and 18 patients had personal histories or symptoms of asthma, hay fever, or hives, in addition to the atopic dermatitis.

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4. Pincus, G., and Elmadjian, F.: The Lymphocyte Response to Heat Stress in Normal and Psychotic Subjects, J. Clin. Endocrinol. **6**:295, 1946.

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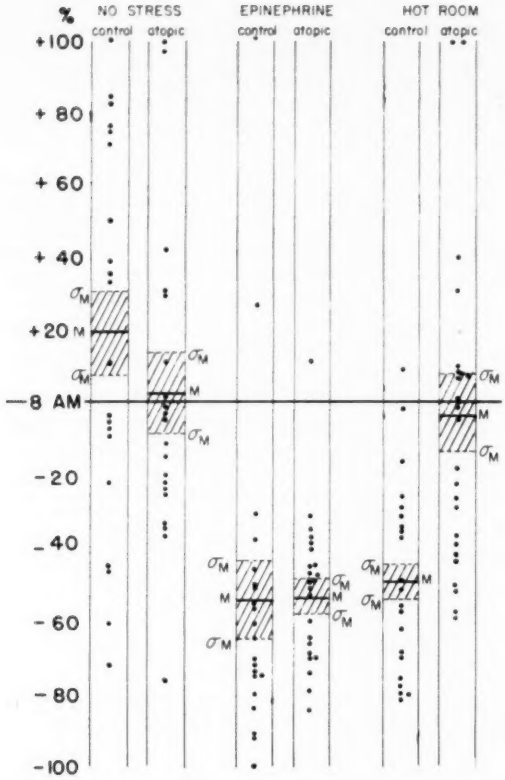

Chart 1.—Eosinophile response expressed as per cent of 8 a. m. level. The key to symbols is as follows: *M*, mean (average); σ_M, standard error of mean; dot, individual response.

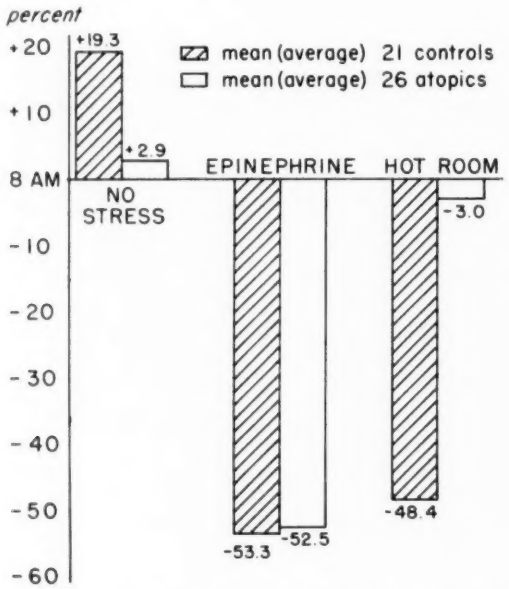

Chart 2.—Eosinophile count expressed as per cent of 8 a. m. level.

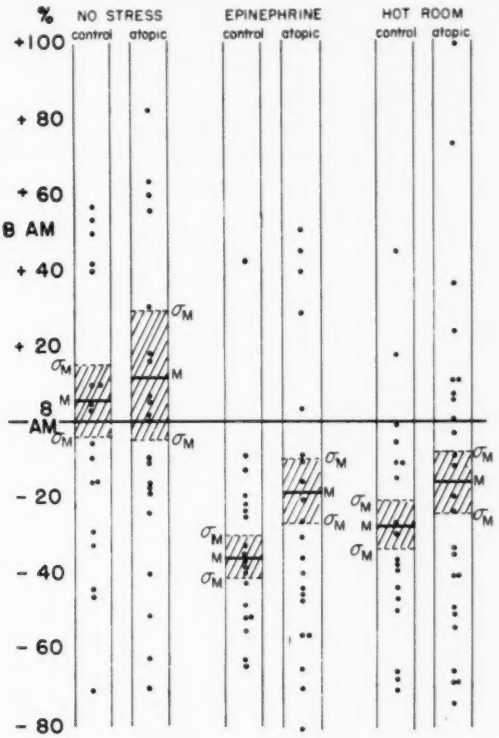

Chart 3.—Distribution of lymphocyte-neutrophile response as per cent of 8 a. m. level. The key to symbols is as follows: *M*, mean (average); σ_M, standard error of mean; dot, individual response.

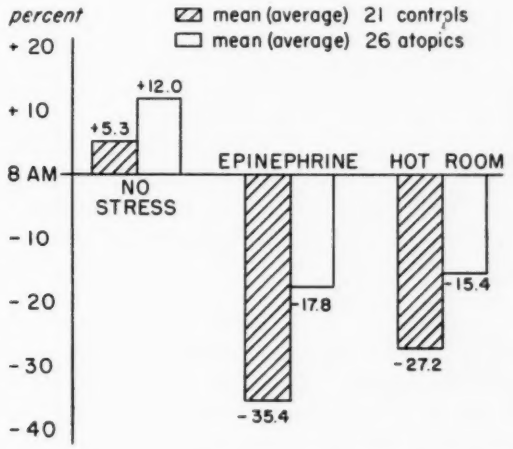

Chart 4.—Lymphocyte-neutrophile ratio expressed as per cent of 8 a. m. level.

RESULTS

Eosinopenic Index.—Chart 1 shows the raw scores for normal subjects and those with atopic dermatitis arranged in a scattergram, with the mean (average) and standard error of the mean indicated on each test procedure. Each "score" represents the per cent change in eosinophile count at 12:15 p. m. from the base level at 8 a. m. While this chart shows the difference in the "mean" responses of all groups after the various tests, it also shows clearly the wide variations in response within each group. Chart 2 has been prepared to show more clearly the "mean" results of all tests. The difference between controls (+19.3%) and atopic patients (+2.9%) on the "dry run" is not statistically significant, while the response of the two groups to epinephrine stimulation is almost identical (—53.3% and —52.5%) and constitutes a "normal" eosinopenic index as reported by Thorn.[3] The difference in response of the two groups to hot room (—48.4%, control; —3%, atopic) is obvious and, upon statistical analysis, is significant beyond the 1-1000 level of confidence with a *t* value of 3.721 for 40 degrees of freedom. This chart shows clearly the principal finding reported in this paper, namely, that atopic persons do not have a normal eosinopenic response to the stress situation of hot-room exposure. This lack of response was a characteristic of the group as a whole, but there were individual exceptions, as shown in Chart 1. There was no correlation between the severity of the disease process and the response to stress.

Lymphocyte-Neutrophile Ratio.—Chart 3 shows the individual variations in lymphocyte-neutrophile ratio arranged in a scattergram. It will be noted that both control and atopic patients show a slight rise in mean values after "no stress" (5.3% and 12%). After epinephrine treatment, both controls and atopic patients showed a drop in ratio (—35.4% and —17.8%), indicating lymphopenia and neutrophilic leucocytosis. After hot-room stress, similar responses were seen (—27.2% and —15.4%). While these shifts in mean indicate a trend, individual fluctuations are so widely scattered, as shown in Chart 3, that the only statistical significance in the data is that atopic persons are more variable with "dry run" and epinephrine treatment than controls, but not under hot-room stress. There is no statistically significant difference in response between the two groups, or between the three tests, except that normal persons show the expected significant drop after hot-room exposure and epinephrine injection. Chart 4 shows the changes in the lymphocyte-neutrophile ratio in block form. The difference between the controls and atopic patients following epinephrine treatment (—35.4% and —17.8%) is shown more clearly. While this difference does not have a high level of significance, it does have a *t* value of 1.72 for 40 degrees of freedom, which places it within the 10% level of confidence, and suggests that perhaps the atopic group, as measured by changes in the lymphocyte-neutrophile ratio, does not respond normally to exogenous epinephrine.

COMMENT

From our results it appears that patients with atopic dermatitis have an intact and properly functioning pituitary-adrenocortical mechanism. Both the control subjects and the atopic patients responded normally to epinephrine, as measured by the eosinopenic index. The lymphocyte-neutrophile ratio was also depressed by the epinephrine, although in this test the response of the atopic group may be

abnormal. Following hot-room stress, there was hardly any depression of the eosinophile count for the atopic group as a whole, although a few members of the group had a normal response. This failure of response of the atopic group to a standard stress situation is, upon statistical analysis, significant at the highest level of confidence. Since, as we have demonstrated, the pituitary and adrenal cortex respond normally to exogenous epinephrine, it may be inferred that the cause of the abnormal response in these patients is in the higher brain centers or in the adrenal medulla. Our results do not permit localization of this defect, nor do they afford any evidence as to the mechanism by which the stress response is blocked.

It has been common knowledge for many years that patients with the atopic diathesis can be precipitated into an acute exacerbation by a variety of emotional stimuli. In this connection, many investigators have attempted to define more sharply the mental make-up of these persons, with the thought that they may exhibit a specific emotional pattern. However, during this same period, it has also been demonstrated that many other factors may precipitate an exacerbation in these patients. These factors include all types of physical stress, a variety of acute infections, virus as well as bacterial, and specific allergic incidents. These precipitating factors all have a common denominator in that they all initiate the alarm reaction of normal persons. This reaction is more or less nonspecific in that the physiologic changes which take place are the same, irrespective of the type of stimulus which triggers the mechanism. Our results therefore suggest that further research in this disease will be more productive if it is directed towards clarifying the cause of the faulty alarm-reaction response to stress.

We have previously postulated [1] that the defect in these patients may be located in the hypothalamus, the higher brain centers, or the adrenal medulla. Irrespective of its location, there is considerable evidence that it is not an irreversible mechanism. It is well known that persons with this complex, at times, do respond to treatment or undergo spontaneous remission and may remain normal for years. Furthermore, the disease is one of youth and early adulthood and, from a symptomatic level, tends to disappear around the middle thirties. The recent advent of corticotropin (ACTH) and cortisone offers, for the first time, specific medications which consistently influence the clinical course of the disease. Twenty-four of the patients in this series were subsequently treated with cortisone,[6] and all responded dramatically while under therapy. In the past the medical attitude toward the atopic diathesis has been one of pessimism and confusion. Now, with the demonstration of a fault in the alarm-reaction response, with the previous evidence of spontaneous remission and modification with age, and with the research stimulating discovery of drugs which consistently influence the disease process favorably, new hope for the eventual solution of this problem is warranted.

SUMMARY

The alarm-reaction response has been studied in a group of 27 classic atopic patients following an injection of epinephrine and an artificially applied stress situation (one hour in a "hot room").

6. Sternberg, T. H.; Newcomer, V. D., and Linden, I. H.: Use of Cortisone in Atopic Dermatitis, to be published.

The atopic patients were found to respond with a normal eosinopenic index following administration of exogenous epinephrine, indicating that their pituitary gland and adrenal cortex are capable of normal function.

Following the hot-room stress, the atopic patients as a group did not show a normal alarm reaction. This failure to react was significant at a high level of confidence.

The implications of this finding are discussed.

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ABSTRACT OF DISCUSSION

Dr. J. Lamar Callaway, Durham, N. C.: I want to take this opportunity to compliment Dr. Sternberg and Dr. Zimmerman on their fine investigation of the eczema-asthma-hay-fever diathesis. The data they have presented are significant, and their observations that patients with atopic eczema show no fall in the eosinophile count as contrasted with a normal fall in the eosinophile count in normal persons is striking.

Since all disease processes have some difference in adrenal pituitary function, one must use some caution in interpreting results, and I am sure that Dr. Sternberg and Dr. Zimmerman would be the first to agree. Although their experiment was well controlled and there was a difference in the eosinophile response, this single factor does not necessarily prove that atopic eczema is a disease of adaptation.

It may be significant that the atopic persons stayed in the hot room, whereas, some of the normal persons did not. Was this a masochistic tendency and not necessarily a block in the hypothalamus or in some of the higher centers?

Pincus has shown that schizophrenics do not have a normal eosinophile response following stress, and this is presumed to be due to some high brain centers which are at fault. In addition, certain malignant conditions and patients with malnutrition respond poorly as far as eosinopenia is concerned. Further, it has been shown that epinephrine will produce an eosinopenia even in adrenalectomized and hypophysectomized rats. It would have been interesting to study the 17-ketosteroid levels in this group of patients, and now that Dr. Sternberg and Dr. Zimmerman have pointed the way, I hope that someone will carry on such an investigation.

One extremely important experiment should be performed, namely, that of the production of nonpsychologic and nonpainful stress. This would tend to get away from any psychologic or masochistic factors. Perhaps the use of intravenous typhoid vaccine might be a suitable method, but even this might possibly carry with it some psychologic factors from the febrile response.

My experience with corticotropin and cortisone has been similar to that of Dr. Sternberg, and, incidentally, it seems to me that it poses quite a contradiction to our usual thinking. Since atopic persons respond to exogenous epinephrine with a normal eosinopenic index and therefore must have an adrenal cortex which is capable of functioning satisfactorily, I have wondered why corticotropin or cortisone is particularly helpful. However, I agree entirely with Dr. Sternberg that during the time that the patients are being treated with corticotropin or cortisone there is marked improvement in their cutaneous lesions.

Dr. Sternberg has emphasized that the emotional-stress factor is just as significant as other trigger factors, such as virus infections, physical stress, and pyogenic infections, in producing a flare in atopic persons.

These fundamental observations of Dr. Sternberg and Dr. Zimmerman have carried us a long way toward a better understanding of the eczema-asthma-hay-fever problem, and whether or not this conforms completely to the Selye alarm reaction, it is a most significant first-screening observation and a step forward in the solution of one of the most difficult problems in dermatology. I shall look forward with much anticipation to continued basic investigations by Dr. Sternberg and his associates.

Dr. M. B. Sulzberger, New York: I was delighted to see Dr. Sternberg's approach to objective methods for measuring the way in which patients with atopic dermatitis respond to stress. I am sure that all of us have been looking for such means of measurement.

I would like to say that the abnormal response of patients with atopic dermatitis is, of course, not an entirely new finding. All of us recall that it harks back to Vidal's hemoclastic crisis

and to the excellent Swiss work of Brack in relation to the abnormal response of people with atopic syndromes to the injection of such things as pilocarpine, atropine, and epinephrine, as well as the response of their blood elements to the ingestion of various foods. This work of Sternberg's is a step forward, however, because, I believe, it brings us into a modern area for the study of these responses.

It interested me particularly that these patients reacted abnormally in the hot room, that it was that particular form of stress which brought out their flaw most clearly and most significantly. The first reason for my particular interest is that this finding corresponds so perfectly with our clinical observations that these patients in general do not stand heat and humidity well. In other words, this flaw of patients with atopic dermatitis is brought out also in their clinical responses to their environment. The second reason for my particular interest in the abnormal response of patients with atopic dermatitis to the hot room is our observation that these patients do not sweat normally. As a rule they have plugging and occlusions of the sweat glands over large areas. This has been shown not only by Dr. Franz Herrmann and the group with which I am connected but has also by Pillsbury, Shelley, Horvath and his coworkers in Philadelphia, and by others. These studies of atopic dermatitis all show that the sweat glands are plugged over very extensive areas of the skin. This could quite naturally account for their abnormal responses to the stress of the hot room.

I should like to ask Dr. Sternberg whether he would not consider adding to his list of possible locations of what I might call "the atopic flaw," the flaw in the sweat apparatus of the skin itself. I think it possible that the main flaw or weakness in these patients might reside not in the hypothalamus, the pituitary-cortical axis, or the other areas but actually in the temperature-regulating end-organ of the skin itself.

As I said, I think that Dr. Sternberg's careful studies bring us into a position to study this very important group of cases more accurately and more intensely with modern methods. One thing he could do to test the idea which I have just voiced is to include in his study patients with the atopic syndrome not involving the skin. Many patients with asthma, hay fever, or other atopic diseases not including skin changes would presumably have normal skins and would sweat properly. If my ideas have anything to them at all, then the responses of these patients in the sweat box might be the same as normal persons', despite their being atopic persons. Such a finding would demonstrate the role of the skin organ itself in determining the abnormal responses of atopic dermatitis to environments with high temperatures and humidities.

Perhaps the beneficial action of cortisone and of corticotropin in atopic dermatitis may be brought into relation with these findings. As we have been able to demonstrate, these hormones are very strong stimuli to sweating. When one administers cortisone and corticotropin to a patient, one produces strong sweat response, perhaps strong enough to clear some of the openings of plugged sweat ducts, perhaps able to prevent future plugging, or perhaps able to obviate for some time the need for sweating in the plugged areas.

Dr. Stephen Rothman, Chicago: In our experience corticotropin and cortisone relieve itching dramatically in dry neurodermatitis but do not influence the objective findings, particularly lichenification. It is remarkable that, although lichenification is generally believed to be a reaction to rubbing and scratching, it does not disappear no matter how long the patient is kept free of pruritus with corticotropin.

Along the lines of Dr. Sulzberger's discussion I should like to emphasize that heat stress is probably not a suitable stimulus if one compares reactions of normal persons with those of atopic persons. One hundred degrees and 95% humidity represents a much greater stress for the atopic patient than for a person with normal skin. Any other stress situation would be preferable to heat stress.

Dr. Frank E. Cormia, New York: I assume that Dr. Sternberg is going to continue this type of investigation. If this is true, I have one small suggestion to make, namely, that he utilize the method which has been popularized to a certain extent by Richter, the measurement of electrical skin resistance. This has been shown to change markedly during stress situations. Following stress, the electrical resistance of the skin goes down, and following adaptation, it may rise over a period of time. This is just another tool with which Dr. Sternberg might work.

Dr. Oscar Gans, Frankfurt, Germany: I have always been impressed by the fact that patients suffering from what you call atopic dermatitis get better spontaneously when they are

hospitalized. Very often patients, for all practical purposes, recover within a few weeks' time. They go home to the old environment, sometimes for hours or a few days, only to be returned to the hospital in the old condition. I never could explain this fact.

We always look for some sort of climatic allergy. I wonder whether one can elucidate the possibility that corticotropin and cortisone have a tendency to act more favorably in a patient who is actually kept at rest and has no stress at all.

DR. THOMAS H. STERNBERG, Los Angeles: I wish to thank the discussants. I am glad to see so much interest and comment on this subject. In answer to Dr. Callaway's question as to why some of the controls left the hot room whereas the atopic patients did not, I believe, or at least I did, that most atopic patients were under the impression that these studies would in some way benefit their condition, and, therefore, they had a motive for sticking it out no matter how uncomfortable they were. Many of them were exceptionally uncomfortable, which leads into the next point, that Dr. Sulzberger raised, the question of sweating. It certainly was true that most of these patients did not appear to have a proper sweat response, and, as I mentioned in the paper, many were subsequently treated with cortisone. During cortisone treatment a number of the patients volunteered the information that they were sweating for the first time in years.

Our failure to study scientifically the sweat response is a defect in experimental design which was not appreciated until after we were well along into the study. We are now taking steps to compensate for this oversight. We are also trying other stresses, a point brought up by Dr. Rothman. In cooperation with Dr. Roy Dorcas, professor of psychology at the University of California at Los Angeles, we are reproducing previous emotional situations under hypnosis and measuring the response to that type of stress which does not involve the skin as an end organ. However, I would agree with Dr. Sulzberger that, at this point, we cannot eliminate the skin as a possible source of fault in these persons, because perhaps in some way it does not transmit the stress situation properly to the higher centers.

In answer to Dr. Cormia's point about skin resistance to an electrical current, such studies have been carried on, mainly by psychologists, since 1898. The phenomenon is referred to as the P.G.R. (psychogalvanic reflex). The electrical resistance of the skin disappears or decreases after a variety of emotional stimuli, to reappear in a short period. The P.G.R. is also probably associated with the secretion of sweat. It does offer considerable possibilities as an investigative procedure.

To get back to Dr. Rothman's comment, 24 of these patients were subsequently treated with cortisone. They all had severe dermatitis. They were selected for treatment because they did. They all responded to adequate treatment, but they all required rather large maintenance dosage to prevent relapse.

PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE IN DISEASES OF THE SKIN

II. Allergic and Other Dermatoses; Report of Sixty-Seven Cases

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NEW YORK

THE STRIKING effects of cortisone (compound E) and corticotropin (ACTH) in the control of diseases affecting mesenchymal and other tissues and on the hypersensitivity reaction have been described.[1] These reports have outlined the results of therapy with these hormones, as well as the complications most frequently encountered. They also have emphasized the rebound phenomenon following therapy and the physiologic effects of these potent corticosteroids.

As the mechanism of action of these hormones is not well understood, it is virtually impossible to predict what diseases they may affect favorably. In order to obtain a spectrum of their usefulness, it is necessary to treat a number of patients with the severe dermatoses that are refractory to current forms of therapy. The following case reports are presented in the hope of adding some pertinent information to the data now being assembled by other investigators.

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† Dr. Hopkins died Feb. 27, 1951.

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Merck & Company, Inc., Rahway, N. J., supplied much of the cortisone used in these studies.

1. (*a*) Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950. (*b*) Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dihydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **24**:181, 1949. (*c*) Pituitary-Adrenal Function: Symposium, edited by R. C. Christman, Washington, D. C., American Association for the Advancement of Science, 1951. (*d*) Bordley, J. E., and others: Preliminary Observations on the Effect of ACTH in Allergic Diseases, Bull. Johns Hopkins Hosp. **87**:396, 1950. (*e*) Thorn, G. W., and others: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783, 824, and 865, 1950. (*f*) Carey, R. A.; Harvey, A. M.; Howard, J. E., and Wagley, P. F.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Drug Hypersensitivity Reactions, Bull. Johns Hopkins Hosp. **87**:354, 1950. (*g*) Randolph, T. G., and Rollins, J. B.: Adrenocorticotropic Hormone (ACTH): Its Effect in Atopic Dermatitis, Ann. Allergy **9**:1, 1951. (*h*) Cannon, A. B., and others: Pituitary Adrenocorticotropic Hormone (ACTH) and Cortisone in Diseases of the Skin: I. Pemphigus Vulgaris and Other Bullous Dermatoses, J. A. M. A. **145**:201 (Jan. 27) 1951.

CASE SELECTION AND ROUTINE STUDIES

The first group comprises 42 patients with allergic dermatoses on whom previous study had shown that the skin eruption was caused or accentuated by the administration of a specific substance to which the patient had become sensitive.

The second group of 25 patients includes 11 with the so-called collagen diseases; 3 with neoplastic diseases involving the skin; 9 with inflammatory reactions of the skin of unknown cause; 1 with total alopecia, and 1 with benign acanthosis nigricans.

So far as indicated, the pretreatment clinical and laboratory studies described in our previous paper [1b] were carried out. In the earlier phases of this study eosinophil counts were done immediately before corticosteroid therapy and four hours later. Later on, when it became apparent that the eosinophil response was not necessarily a true index of the clinical response to be expected, use of the test as a routine procedure was discontinued.

At first when treatment with corticotropin was initiated, 100 mg. daily in four divided doses for one to three days was usually employed. When therapy was started with cortisone, single daily intramuscular injections of 300 mg. the first day, 200 mg. the second day, and 100 mg. the third day were given. Later, particularly in the patients with drug eruptions, the hormone preparations were used simultaneously. Duration of therapy varied from 1 day to 47 weeks. Cortisone in reduced dosage was usually given for maintenance, to some daily but to many patients in an interrupted schedule. Generally speaking, optimal dosage and duration of therapy varied within wide limits and necessarily had to be adjusted to the clinical response.

CLINICAL RESULTS

Group 1: Allergic Dermatoses.—In this group of 42 cases intrinsic and extrinsic sensitization of the skin by known allergic excitants was present. The intrinsic reactions include atopic (allergic) eczema, which is initially a gastrointestinal allergy to foods with the dermis acting as the shock organ; urticaria, in which the vascular endothelium is sensitized, and drug eruptions, in which either tissue may become allergic. Dermatitis venenata is the form of extrinsic sensitization in which the epidermis is primarily involved. The beneficial effects of cortisone and corticotropin, acting on the abnormal tissue reactions that are thought to follow the union of antigen and antibody, are given in the following tables.

Allergic Eczema: As shown in Table 1, eight patients had severe relapses of long-standing eczema characterized by lichenified eczematous patches in the antecubital and popliteal areas, diffuse erythematous vesicular areas over the face and neck, and patches of excoriated dermatitis on the trunk and extremities. The extensive involvement of the skin and intolerable spasmodic itching required hospital care. The patients gave the usual personal and family history of other allergies and were familiar with a variety of foods, inhalants, and substances with which they came in contact, and with emotional factors which intensified their symptoms. Within one to four days after a daily dose of 100 mg. of corticotropin or 200 mg. of cortisone they felt "like a different person." Pruritus was minimal; sleep was not interrupted; new lesions did not appear, and the dermatitis began to subside. With continued threapy progress was less rapid but definite. The skin of three patients cleared. That of the remaining five was remarkably improved. Shortly

TABLE 1.—*Course in Chronic Atopic (Allergic) Eczema in Adults*

Patient	Duration		Treatment			Results		Course	% Eosinophils		Complications
	Present Attack, Mo.	Of Disease, Yr.	Time Treated	Total Dose, Gm.		Significant Relief, Days	Maximum Effect, Days		Before Treatment	After Treatment	
				Cortisone	ACTH						
F. G.	10	10	9 mo.	8.0	3.0	2	8	About clear; relapse in 3 days; retreated, good response; four relapses on stopping therapy	18	2	30-lb. weight gain; suspected appendicitis; abscess at injection site; frequent (4 attacks) skin infection; all cleared on stopping therapy
J. R.	4	24	3 wk.	2.0	...	2	22	About clear; severe relapse in 1 wk.	18	7	See case report
D. K.	2	25	8 mo.	6.0	1.0	2	5	Excellent response; relapse in 2 wk.; retreated; minimal eczema with 25 mg. daily	24	3	20-lb. weight gain; three attacks lymphangitis of legs
H. F.	8	39	1 mo.	3.2	...	4	21	Dramatic temporary clearing of skin; partial relapse 2 mo. later	7	1	Temporary euphoria; parotid gland infection
I. R.	4	22	4 mo.	4.5	...	4	9	Clear in 2 wk.; relapse in 5 days; retreated; minimal eczema with 50 mg. daily	4	1	Edema responded to low-salt diet; furuncles
M. C.	3	16	4 mo.	6.0	...	3	7	Clear in 2 wk.; relapse in 4 days; re-treated; clear if given 50-100 mg. biweekly	18	4	12-lb. weight gain; abscesses at injection sites; hematemesis (roentgenogram normal)
C. A.	12	24	2 mo.	3.0	...	4	30	Definite improvement; partial relapse in 2 wk.	9	2	Pustular skin infection
T. O.	3	18	1 wk.	1.0	...	1	4	Marked improvement; relapse in 4 days	11	3	.....

after therapy relapses of varying intensity occurred in all. Four were re-treated and then maintenance doses of 25 to 50 mg. of cortisone were given almost daily for varying lengths of time. Only so long as the drug was given was the eczema minimal or absent. While receiving therapy, two patients were able to eat with impunity foods which had formerly produced an exacerbation, and three were not. Chemical studies of the blood revealed no significant changes. A consistent reduction in eosinophils paralleled the clinical improvement, but eosinophilia recurred after therapy. Repetition of skin tests, during and directly following treatment, with allergens causing reactions before treatment produced conflicting results. Biopsy incisions made directly before and during treatment healed promptly, and only one became infected.

The most troublesome complication was the lack of resistance to pyogenic infections. This resulted in abscesses at the site of injection, a parotid gland infection, and pustular skin infections during or directly following the interruption of therapy. It is difficult to evaluate the pain in the right lower abdominal quadrant that occurred in one patient with a normal venous clotting time and the hematemesis in another without roentgenographic evidence of gastrointestinal damage. In neither patient did the symptoms recur when treatment was reinstituted in smaller doses. A slow but pronounced gain in weight was noted in three patients and persisted until therapy was discontinued.

One patient (D. K.) with recurrent Staphylococcus lymphangitis of the legs was successfully immunized with Staphylococcus toxoid while receiving cortisone.

The temporary remission of eczema, the ability of some patients to ingest known allergens, and the drop in eosinophils while they were receiving either drug have been reported previously in six patients.[2]

From a study of this limited number of patients, it seems that the use of corticotropin or cortisone in treatment of atopic eczema is justified if during its administration it is also possible to hyposensitize the patient to the various substances to which he is allergic and to adjust the emotional factors intensifying his disease.

Illustrative case: The eczema of Patient J. R., aged 24, a salesman, began on the seventh day of life and persisted until the age of 10. During adolescence his skin was clear, but for the past seven years he had had remissions only during the summer. The patient had been married a year and because of his illness was in financial distress. There was a family history of eczema. Chocolate and milk had caused his eczema to flare. On admission he was "worn out" and extremely nervous. The skin showed a severe lichenified dermatitis covering the face, neck, upper part of the chest, and flexor surfaces of the arms, wrists, and dorsa of the hands. There was less severe involvement of the thighs and popliteal areas. There were numerous deep excoriations, fissures, and areas of slight exudation. Histologic examination of the involved skin showed chronic dermatitis. Physical and laboratory examinations revealed no abnormalities except 18% eosinophils (865 per cubic millimeter).

The patient was put on a diet excluding the common allergens and was given 300 mg. of cortisone the first day and 200 mg. the second day. In 48 hours there was great reduction in itching and inflammation of the skin. Within a week after he received 1,250 mg. of cortisone the eosinophil count had dropped to 462 per cubic millimeter and the skin improved so remarkably that milk, wheat, and eggs were added to the diet. Within 24 hours there was a sharp exacerbation of the eczema. The three foods were withdrawn, and cortisone treatment was

2. Randolph and Rollins.[1g] Kanee, B.; Grant, J. H. B.; Mallek, J., and Eden, J.: ACTH in Atopic Dermatitis (Infantile Eczema) and Asthma, Canad. M. A. J. **62**:428, 1950. Rackemann, F. M.: Allergy—Histamine and ACTH, A. M. A. Arch. Int. Med. **87**:598 (April) 1951.

continued. In 10 days after administration of a total of 2 gm. of cortisone the skin was dry and clear except for slight thickening in the flexures. One week after therapy the eczema had returned and was severer than on admission. Before treatment intradermal tests showed strong reactions to chocolate, dust, and wool. After he was given 1.5 gm. of cortisone, only the reaction to wool persisted. Three days after therapy there was a strong reaction to chocolate only.

Urticaria (Not Produced by Drugs): Table 2 lists three patients who received therapy for urticaria. In the two in whom it was due to food there had been no sustained response to treatment with epinephrine, calcium gluconate, or diphenhydramine (benadryl®) hydrochloride. The hives were giant and both superficial and deep. The intense itching made it impossible for the patients to sleep. The response to either corticotropin or cortisone therapy was equally dramatic, with symptomatic relief in 24 hours; the skin was entirely normal in two and four days. A similar experience with a patient having urticaria due to food is reported by Cohn.[3] However, there are a few reports of urticaria and anaphylactic reactions following the administration of corticotropin,[1a] which may be due to sensitivity to pork. The third patient was of particular interest because either localized or generalized hives could be produced routinely. This afforded an opportunity to

TABLE 2.—*Course of Urticaria (Not Due to Drugs)*

Patient	Duration	Location	Cause	Therapy			Result
				Drug	Total Amount, Gm.	Days Treated	
E. A.	50 yr. (intermittent)	Localized and generalized	Sunlight	Cortisone	3.0	16	No improvement; see case report
M. B.	5 days	Generalized	Food	ACTH	0.15	2	Well in 2 days
C. C.	9 days	Generalized	Food	Cortisone	0.9	3	Well in 4 days

study the inhibition of localized hives by treatment with cortisone and to attempt rapid tolerance to sunlight.

Illustrative case: E. A.,[4] a housewife, aged 57, in excellent general health, had to become a recluse during the summer months because of urticaria following exposure to sunlight, which had occurred for as long as she could remember. Minimal exposure of the hands and arms to bright sunlight, direct or reflected, produced on these areas itching hives which persisted a few hours. Exposure of the same areas for 10 minutes caused generalized urticaria and a headache which lasted about 24 hours. More prolonged exposure also caused severe palpitation, a sense of thoracic constriction, syncope, and on two occasions profound shock. With light-transmitting filters, the patient's sensitivity was found to be between 4,000 and 5,000 A. An isolated wheal was produced when the patient's arm was exposed for 45 seconds to a 300-watt Mazda projection bulb, which emits those wave lengths. This sensitivity to sunlight and to a specific wave length was easily transferred to normal persons by intradermal injection of the patient's serum. Oral administration of tripelennamine (pyribenzamine®) hydrochloride and use of vitamin A cream locally afforded the patient some protection. The physical examination revealed an essentially normal condition, and there was no history of other sensitivities. Exhaustive laboratory studies, which included porphyrin, carotene, and vitamin A determinations, gave normal results. The patient remained in the hospital 16 days, during which she received 3 gm. of cortisone, the dosage varying from 300 to 100 mg. daily. During therapy the time required to induce local

3. Cohn, in Proceedings of the First Clinical ACTH Conference.[1a]

4. This patient was presented at the meeting of the Section on Dermatology and Syphilology, New York Academy of Medicine, New York, March, 1950.

TABLE 3.—*Course in Drug Eruptions*

Patient	Character of Eruption	Duration	Cause	Therapy, Mg.		Results	Comments
				Cortisone	ACTH		
H. S.	Generalized urticaria (serum sickness type)	2 days	Penicillin	400	...	Well in 4 days	Striking symptomatic relief in 24 hr.
G. F.	Generalized urticaria (serum sickness type)	8 days	Penicillin	600	...	Well in 2 days	Striking symptomatic relief in 24 hr.
S. H.	Generalized urticaria (serum sickness type)	8 days	Penicillin	...	112	Urticaria gone in 2 days	Elevated erythrocyte sedimentation rate and arthralgia persisted one week
T. M.	Generalized urticaria (serum sickness type)	7 days	Penicillin	1,000	75	Well in 1 wk.	See case report
C. G.	Generalized urticaria (serum sickness type)	7 days	Penicillin	950	150	Well in 4 days	Dramatic response in 24 hr.
G. R.	Generalized urticaria (serum sickness type)	2 days	Penicillin	600	150	Well in 2 days	Dramatic response in 24 hr.
M. R.	Generalized urticaria (serum sickness type)	8 days	Penicillin	600	150	Well in 2 days	Dramatic response in 24 hr.
S. S.	Generalized urticaria (serum sickness type)	3 days	Penicillin	900	150	Well in 3 days	Dramatic response in 36 hr.
E. G.	Generalized urticaria (serum sickness type)	42 days	Penicillin	1,500	75	Well in 8 days	Early symptomatic relief, few hives for 1 wk.
T. J.	Generalized urticaria (serum sickness type)	5 days	Penicillin; sulfadiazine; streptomycin	675	75	Well in 4 days	Triple medication for pyelitis; dramatic relief in 18 hr.
M. W.	Generalized urticaria (serum sickness type)	2 days	Tetanus antitoxin	600	150	Well in 2 days	Edema of larynx gone in 24 hr.
N. W.	Edema of face and neck; dermatitis of penis	2 days	Penicillin	300	...	Well in 4 days	.....
M. D.	Erythema nodosum	5 days	Chloramphenicol; aureomycin	800	300	Well in 9 days	Acutely ill; no relief from acetylsalicylic acid or antihistaminics; symptomatic relief in 24 hr.
R. C.	Extensive acute exudative dermatitis; marked edema of face	1 day	Poison ivy injections	300	...	Well in 1 wk.	Generalized eruption following injection during mild attack of poison ivy; significant relief from itching in 24 hr.; edema gone in 48 hr.
M. M.	Marked vesicular dermatitis, trunk and extremities	7 wk.	Poison ivy injections	1,800	...	Clear in 5 days; relapse	History of 5 injections for poison ivy; patch test to ivy on 6th day followed by severe recurrence of dermatitis
M. A.	Intolerable pruritus and papular eruption of trunk and thighs	5 wk.	Procaine; bromides	1,800	...	Clear in 2 wk.	Cleared in 5 days; relapse 8th day; treatment resumed for 5 days
W. E.	Generalized erythroderma with intolerable pruritus	4 mo.	Gold	1,900	...	Clear in 4 wk.	History of 50 injections for arthritis; no sustained effect on arthritis
H. P.	Generalized chronic exudative dermatitis	7 mo.	Sulfadiazine; streptomycin	2,250	...	Clear in 3 wk.	Significant relief in 48 hr.; hypertension after 1.2 gm.; relapse; re-treated with smaller doses
O. W.	Generalized exfoliative erythroderma with dermatopathic lymphadenitis	2 wk.	Sulfanilamide	1,500	1,025	About clear in 12 wk.	Acutely ill; dramatic response 3 days; marked anemia; relapse; re-treated; clear in 4 wk.; hair turned white
W. S.	Stasis dermatitis of legs Diffuse erythematous papular dermatitis	2 yr. 10 wk.	Stramonium?; penicillin	...	650	About clear in 8 days	Prompt relief; entirely normal in 2 mo.
E. T.	Generalized acute vesicular and hemorrhagic dermatitis	4 days	Penicillin	1,300	300	About clear in 6 days	Temperature 104.4 F.; stomatitis; dramatic response; afebrile in 12 hr.

whealing increased progressively, so that 10 minutes was necessary by the 10th day. As the dose of cortisone was decreased, so was the time required to produce a wheal, and a week following therapy only one minute was needed.

Passive transfer of sensitivity was still possible during and after therapy. Unfortunately, there was no consistent clinical improvement during or following administration of the drug, and the patient exhibited a mild depression which lasted about two months.

The increase in the time required to produce local whealing while the patient was under treatment suggests that if it had been possible to continue the administration of cortisone increased resistance to sunlight might have followed. Carey [1f] effected partial desensitization to drugs in patients receiving corticotropin therapy.

Drug Eruptions: Table 3 lists 21 patients who had a variety of eruptions after the oral or intramuscular administration of antibiotics, Rhus toxicodendron, or other drugs. All became well after administration of cortisone or corticotropin or a combination of the two. One (M. M.) had a severe recurrence. This patient was the only one challenged with the drug to which she was sensitive while receiving cortisone therapy. One year later a dramatic response occurred to cortisone and corticotropin given for a persistent dermatitis which followed attempted desensitization to Rhus toxicodendron and procaine injections.

More than one-half the sensitizations were due to penicillin. The commonest, the serum sickness type, responded dramatically to hormone therapy. This response is similar to that in eight cases previously reported.[5] Most of the patients in our series gave a history of having had penicillin prior to the present course. The reaction occurred either during penicillin administration or about a week later and became increasingly severe. In most there had been no sustained response to treatment with epinephrine or antihistaminic drugs.

On admission they were febrile, covered with giant hives, and had been suffering from insomnia, arthralgia, and intolerable itching for two days to six weeks. The hives tended to be gyrate or annular, with an intense red center and wide blanched borders (Figure). Often they were associated with severe edema of the head, arms, and hands.

Usually within 24 hours of institution of therapy there was a gratifying subsidence of symptoms, and all but one were well within eight days, regardless of the duration. Three of the patients received cortisone only and responded about as quickly as those receiving combined therapy. At present the most effective treatment seems to be 25 mg. of corticotropin every four hours for four to six doses, together with 100 mg. of cortisone three times a day for a day or two. There were no complications. The results compare favorably with those reported by Carey and others.[1f]

Although the duration of serum sickness reaction following penicillin therapy is unpredictable, we have observed its persistence for many weeks or even months. The following patient was of particular interest because he was observed during two attacks. The first, without cortisone and corticotropin treatment, persisted five and one-half weeks, and the second, during which he received this therapy, lasted one week.

Illustrative case: T. M., a 30-year-old veteran with asymptomatic neurosyphilis, had generalized urticaria in 1948, after the first injection of penicillin. In the spring of 1950, to test sensitivity, 10 units of crystalline penicillin was injected intracutaneously in the right forearm.

5. Footnote 1*a*, *d*, and *f*.

A large wheal developed almost immediately. On Feb. 2, 1951, he received 600,000 units of penicillin intramuscularly. Shortly afterward redness and itching appeared on his right arm and persisted 48 hours. Eight days later generalized urticaria developed and became increasingly severe. He was admitted to the hospital Feb. 14, with a temperature elevation to 102 F., swelling and soreness of the throat, generalized painful urticaria, edema of the head, neck, and feet, and swollen, painful joints. After treatment with epinephrine, diphenhydramine hydrochloride, acetylsalicylic acid, and ephedrine, all symptoms except urticaria subsided in 10 days. Transient hives and swelling of the feet continued until March 30. As the Wassermann reactions of the patient's blood and spinal fluid remained strongly positive, he was given 50,000 units of P-92[6] on April 13. No reaction followed, and on April 16 and 18 the dose was repeated. Five hours

Serum-sickness-like reaction of Patient T. M. to penicillin: Large annular wheals with blanched borders; bullous eruption on right arm at site of previous intradermal injection of penicillin, that is, Arthus-like reaction.

after the third injection urticaria developed on the right forearm and was quickly followed by a generalized outbreak. Because of the increasing severity of his symptoms, he was readmitted on April 26 with a duplication of his February symptoms. In addition, bullae were present on the right forearm (Figure) and hemorrhagic wheals on the right wrist. The patient received 75 mg. of corticotropin and 300 mg. of cortisone in divided doses during the first 24 hours, 300 mg. of cortisone daily for the next three days, and 100 mg. on the fourth day. Within 48 hours of the initial dose, the wheals and swelling had decreased greatly and the patient was comfortable. In 72 hours the patient's temperature was normal, the headache and joint pains had

6. P-92 is the penicillin salt of 1, 2 diphenyl-2-hydroxyethylamine ("compenamine").

subsided, and the skin was clear except for moderate erythema and edema of the forearms with crusting at the sites of the bullae. The fourth day two small wheals developed. The fifth day the patient was well except for crusts. This Arthus-like reaction healed within a week, and the patient has had no recurrence of symptoms.

In the fear that the host response to syphilitic infection was also repressed by the hormones,[7] aureomycin therapy was quickly instituted.

The remaining 2 of the 11 patients with serum-sickness-like reactions responded equally well to steroid therapy, although the reaction in the one followed the administration of three antibiotics and in the other injections of tetanus antitoxin.

Hypersensitivity to drugs was expressed by a somewhat localized or generalized inflammation of the skin in the remaining 10 patients. With corticotropin or cortisone therapy, symptomatic relief was striking. In two acutely ill patients a sense of well-being and a return to normal temperature occurred within 36 hours. After two or three days of therapy there was a definite diminution in edema and exudation, with a concomitant relief from itching or pain. Patients with the more generalized eruptions relapsed if treatment with 25 to 50 mg. of either drug was not maintained for a short time after the eruption subsided. The only complication was temporary hypertension in one patient (H. P.) which developed after 200 mg. of cortisone had been given daily for six days. Although the serum sodium and potassium levels were normal, the patient was given a low-sodium diet. Therapy was resumed 4 days later for 10 days. At this time the skin was clear except for residual erythema of the legs, and the blood pressure was 185/90.

The prompt blocking of inflammatory reactions produced by sensitization to iodide, sulfonamides, penicillin, and a cinchoninic acid derivative has been reported.[1d,f] Carey [1f] found it possible partially to desensitize an asthmatic patient to acetylsalicylic acid while administering corticotropin, and after this therapy to give two patients penicillin without further reactions.

The prompt symptomatic relief of drug eruptions following the administration of cortisone or corticotropin is unequivocal. Their use, under controlled conditions in which further administration of the culpable sensitizing drugs is probably unnecessary, seems to have merit. If the patient is in need of the drug to which he is allergic, desensitization as carried out by Carey [1f] is suggested.

Dermatitis Venenata: The 10 patients listed in Table 4 had had an acute, somewhat localized reaction following local medication or contact with other drugs, hair dye, poison ivy, metals, or cosmetics. In five this was followed by a widespread, intensely pruritic vesicular or papular eruption. In addition, two, a pharmacist and a dentist, had localized areas of chronic dermatitis which had recurred for more than 4 and 18 years, respectively. The acute eruptions had been present three days to six weeks. In eight patients there was prompt symptomatic relief within two days after either cortisone or combined therapy. The remaining patient (G. P.) was only moderately improved after receiving 1.4 gm. of cortisone but relapsed when therapy was discontinued. However, there was a dramatic response with 1.05 gm. of corticotropin. Improvement continued with small doses of cortisone. Five patients in whom eruptions had been present 3 days to 6 weeks were well within 10 days. Two received only small amounts of cortisone and the remaining

7. Turner, T. B., and Hollander, D. H.: Cortisone in Experimental Syphilis, Bull. Johns Hopkins Hosp. **87**:505, 1950.

TABLE 4.—*Course in Dermatitis Venenata (Adults)*

Patient	Present Illness	Duration	Therapy, Mg.		Results	Comment
			Cortisone	ACTH		
G. D.	Intense edema and erythema, head, neck.....	5 days	300	...	Well in 5 days	See case report
A. P.	Acute vesicular dermatitis, face, neck.....	6 wk.	900	75	Well in 4 days	Relief in 36 hr.
T. C.	Severe eczematoid dermatitis, trunk, extremities	2 wk.	800	...	Well in 10 days	Exudation stopped in 48 hr.
I. G.	Acute vesicular dermatitis, foot.....	1 mo.	600	175	Well in 1 wk.	.....
	Generalized papular eruption.....	3 wk.				
A. H.	Acute vesicular dermatitis, head, neck.....	2 mo.	2,100	...	Well in 5 wk.	Marked improvement in 1 wk.
	Papular dermatitis, trunk, extremities.....	1 mo.				
E. B.	Acute vesicular dermatitis, axillas.....	3 wk.	1,750	100	Well in 9 wk.	Striking improvement 5 days; relapse; re-treated; good response; maintenance dose 5 wk.
	Generalized papulovesicular dermatitis.....	2 wk.				
F. P.	Acute vesicular dermatitis, hands, arms.....	3 wk.	3,000	400	Well in 3 mo.	Significant relief 2 days; about clear in 3 wk.; two relapses; re-treated; maintenance dose 1 mo.
	Chronic lichenified dermatitis, face, ankles.....	18 yr.*				
G. P.	Chronic lichenified dermatitis, hands.....	4 yr.*	2,600	1,050	Well in 2 mo.	Moderate improvement after cortisone; two relapses; dramatic response to ACTH; maintenance dose 2 wk.; acute Streptococcus infection of hands developed with cortisone therapy
	Generalized vesicular dermatitis.....	3 wk.				
E. O.	Acute edema, head, hands. Vesicular dermatitis, face, neck, hands	3 days	1,500	425	Well in 8 days	Edema of face cleared in 48 hr.; therapy discontinued; no improvement; retreated
P. D.	Localized patches vesicular dermatitis at points of contact with nickel	8 mo.	10% ointment	...	Partial protection	See case report

* Intermittently.

three the combined drugs. The maximum amount given to any one patient was 2.6 gm. of cortisone and 1 gm. of corticotropin. In the remaining three patients there was pronounced early symptomatic relief, but the dermatitis cleared slowly. The effectiveness of the treatment with combined steroids, in this group, is questionable. The only complication was an acute Streptococcus infection of the hands which developed in G. P. while receiving cortisone.

To test the action of cortisone applied locally, one patient (P. D.), in whom dermatitis could be produced regularly with the application of a 5% solution of nickel sulfate, was studied in the following manner: Ten per cent cortisone ointment was rubbed into an area on the left thigh twice daily for one week and the ointment base into the right thigh. Patch tests with the nickel solution were then applied to each thigh for 24 hours. Mild dermatitis developed on the left thigh, and severe dermatitis on the right. Cortisone ointment was then applied twice daily to the latter and the ointment base to the area of mild dermatitis on the left thigh. In a week both areas were clear. This single observation suggests that cortisone applied locally may have some repressive action on allergic inflammatory skin reactions.

The following patient was observed on two occasions after the application of hair dye; the first reactions, without cortisone therapy, persisted three weeks, and the second, with cortisone treatment, lasted five days.

Illustrative case: G. D., aged 50, redyed her hair six days previous to admission. Within a few hours of application, she noted burning and tightness of the scalp which were quickly followed by edema of the eyelids. When she was admitted to the hospital three days later, there were intense edema of the entire head and neck and diffuse erythema of the head, neck, and shoulders. After receiving epinephrine, antihistaminics, and wet dressings for two days without relief, the patient was given 150 mg. of cortisone daily for two days. Within 48 hours the edema was gone, and in five days the skin was entirely normal. After a similar attack five years previously which persisted three weeks, a patch test with the hair dye had given a strongly positive reaction. A day after cortisone therapy the patient was retested, with negative results. Three months after therapy the skin test reaction was again positive. Abolition of the reaction to a haptene during hormone therapy is in agreement with Carey's [1f] reports on atropine sensitivity. One of his patients tolerated challenging doses of atropine while receiving corticotropin in adequate dosage.

Skin Testing During and After Corticosteroid Therapy: The results of skin tests in a few of our patients with allergic eruptions add to the already conflicting experimental and clinical reports. As the modifications of allergic response in the various hosts are probably dependent on the challenging antigen and the quantitative relationship between the doses of antigen and those of the hormones, many more tests will be necessary before arriving at conclusions. In the main, it would seem that neither steroid inhibits the capacity of the epidermal tissue to release histamine or to respond to its intradermal injection, but they do temporarily partially or completely suppress cutaneous reactions to food, inhalants, bacteria, and drugs. The following three exceptions were noted in our patients: In two patients with atopic eczema exhibiting multiple positive skin reactions, only a portion of the reactions to intradermal tests became negative during therapy; the third patient maintained a positive reaction to Staphylococcus toxoid during therapy, although he received 6 gm. of cortisone and 1 gm. of corticotropin. The consensus is that neither drug interferes with antibody production. This view is supported by the ability to transfer light sensitivity passively during and after cortisone therapy in one patient

TABLE 5.—*Course in Collagen Diseases*

Patient	Sex	Age, Yr.	Diagnosis	Lesions, Location and Duration	Treatment: Drug Used	Treatment: Total Dose, Gm.	Treatment: No. of Days Treated	Result
M. P.	F	26	Lupus erythematosus, chronic discoid	Large plaques on nose; smaller lesions over cheeks, forehead and lips; 1½ yr.	Cortisone	3.7	54	Improvement 4th day; subsequent slow involution of lesions; relapse
P. D.	M	27	Lupus erythematosus, chronic discoid	Entire nasal area involved; smaller lesions forehead, cheeks and ears; 3 yr.	Cortisone	4.6	43	Improvement within 48 hr.; no relapse; 5 mo. without therapy
C. L.	F	25	Lupus erythematosus, subacute disseminate	Deep congestive erythema of entire face and neck; diffuse involvement of extremities with scaling, purpuric erythema; 8 mo.	Cortisone	3.0	18	Clearing of eruption; remission lasted 3 wk.; temporary edema
					Cortisone ACTH	4.0 0.4	23 3	Striking improvement in 24 hr.; erythrocyte sedimentation rate and skin about normal in 3 wk.; maintenance dose until acute depression developed
C. M.	F	58	Lupus erythematosus, acute disseminate	Generalized erythema with small bullae on the trunk; large areas of alopecia throughout scalp; 2 mo.	Cortisone	6.675	75	Remission; see case report (C. M.); edema during therapy
J. D.	F	39	Dermatomyositis	Face, trunk, extremities; 16 yr.	Cortisone	2.0	18	No improvement
G. H.	F	38	Sclerodermatomyositis	Face, extremities; 16 mo.	ACTH Cortisone	0.725 1.0	8 9	No objective improvement
H. W.	F	9	Dermatomyositis	Face, extremities, front of chest; 1 yr.	ACTH	0.85	11	Questionable improvement during therapy; developed slight glycosuria
P. D.	F	59	Rheumatoid arthritis with Sjögren's syndrome	Mucous membranes affected; 4 yr.	Cortisone	2.9	16	Exacerbation during first 5 days of treatment
M. H.	F	64	Psoriasis vulgaris and arthritis	Plaques on trunk and extremities; 14 yr.; hands and feet; 9 mo.	ACTH	0.970	17	Psoriasis and arthritis improved slightly
H. S.	M	47	Pustular psoriasis, psoriatic erythroderma, and arthritis	Pustular lesions of palms and soles; 3 yr.; plaques on trunk and extremities; 44 yr.	ACTH Cortisone	1.6 1.4	16 18	No permanent response; see case report (H. S.)
S. S.	F	48	Psoriatic erythroderma and arthritis	Generalized exfoliative dermatitis; 1 yr.; intermittent attacks; 21 yr.	Cortisone	34.0	334	Partial regression of lesions; distinct improvement in arthritis; relapse; prolonged re-treatment with little improvement; complications: moon facies; edema; thrombophlebitis, buttock abscesses

and by the severe exacerbation of dermatitis in another when challenged with the allergen (Rhus toxicodendron) to which she was sensitive.

Group II: Miscellaneous Dermatoses.—Collagen Diseases: In Table 5 are listed 11 patients with so-called collagen vascular disease. The results agree on the whole with those previously reported [8] and point up the need for a more specific remedy.

In two patients with chronic discoid lupus erythematosus there was prompt partial involution of the lesions with cortisone therapy. One patient soon relapsed, but in the second (P. D.) the improvement has persisted during ten months' observation. A third patient (not included in the table) displayed high fever, malaise, joint pains, and leucocytosis 18 hours after the first injection of cortisone. A second injection two days later produced the same response.

Disseminated lupus erythematosus in two patients responded dramatically to corticosteroid therapy. In one (C. L.) with the subacute type there were two complete temporary remissions. After the second, however, she had an acute depression. The patient with the acute disseminate type described below demonstrates the dramatic response to corticosteroids.

Illustrative case: C. M., an Irish housewife aged 59, showed discoid lupus erythematosus on the scalp with alopecia in March, 1949. In June erythematous areas appeared on the face, neck, hands, and right knee. In March, 1950, pronounced palmar lesions and a disseminated scaling erythematous eruption developed, with loss of strength and weight.

On her admission, in July, 1950, the patient was profoundly ill with a scaling erythema over the face and plaques of intense erythema with hemorrhagic bullae on the trunk and extremities. The temperature was 101 F. and the pulse rate 128. The heart was slightly enlarged with a systolic murmur over the apex. The erythrocyte sedimentation rate was 72 mm. per hour (Westergren). There were 3,560 white blood cells, with a normal differential count, and 3,500,000 red blood cells. The total protein was 6.7 gm., with a ratio of 1. No Hargraves (L. E.) cells were found. The urine showed a 2+ reaction for albumin, with many white blood cells and an occasional red blood cell. Cephalin flocculation was 2+. Biopsy specimens from the scalp and from a bullous lesion on the chest were diagnosed as showing lupus erythematosus. The clinical diagnosis at this time was acute disseminated lupus erythematosus.

After admission her condition deteriorated rapidly. Cardiac decompensation developed, with incomplete heart block and pleural effusion. She became disoriented, incontinent, and unable to retain food or medicaments. Digitalization was carried out; chloramphenicol (chloromycetin®) and penicillin were administered. On July 27, 300 mg. of cortisone was given; 200 mg. was administered daily thereafter through the 13th day, and 100 mg. through the 50th day. The dose was then reduced to 100 mg. every second or third day for the remainder of the hospital stay. On the fourth day of therapy the temperature spiked to 107.6 F. In two weeks skin lesions had disappeared except on the soles, palms, and scalp. By the 20th day the patient was alert. Intense edema of the legs was present during the fourth to eighth weeks of therapy.

She was discharged afebrile and walking nine weeks after the beginning of therapy. The erythrocyte sedimentation rate had fallen to 11 mm. on one occasion, but was 45 mm. on discharge. The hair was regrowing, and the skin was clear.

The patient maintained her improvement for two months following discharge, during which time she received 100 mg. of cortisone a week. Two months after this therapy was discontinued,

8. Carey, R. A.; Harvey, A. M., and Howard, J. E.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on the Course of Disseminated Lupus Erythematosus and Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **87**:425, 1950. Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**:229, 1950. Brunsting, L. A.; Slocumb, C. H., and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus, A. M. A. Arch. Dermat. & Syph. **63**:29 (Jan.) 1951. Footnote 1*a*.

her sedimentation rate was 97 mm. and there was moderate loss of strength. An attack of herpes zoster resulted in severe postherpes pain. Ten months after the last injection there were no cutaneous manifestations.

Three patients with dermatomyositis received treatment with corticotropin or cortisone or both. None of these showed any improvement despite apparently adequate dosage. In Patient H. W. the total creatine excretion and the erythrocyte sedimentation rate fell to nearly normal levels, but this was not accompanied with clinical benefit. Remissions in this disease lasting as long as four months have been reported [1a] without therapy.

One patient (P. D.) with rheumatoid arthritis and Sjögren's syndrome (keratoconjunctivitis sicca) of four years' duration was given relatively large doses of cortisone (2,900 mg. in 16 days) with no sign of improvement. This failure to respond was unexpected, since Ragan [9] and others [1a] have observed good results.

Three patients with three different types of psoriatic lesions accompanied with rheumatoid arthritis were treated with corticotropin or cortisone. Although the psoriatic lesions in each patient showed temporary improvement, relatively large doses of the hormones were required, and maintenance of the improvement was extremely difficult. Cessation of therapy was followed by prompt relapse of the psoriasis in each case. The severity of these exacerbations was striking and suggests that after corticosteroid therapy the psoriatic patient may be left in a state worse than before treatment. Irons and co-workers [10] have indicated that chronic psoriasis may respond to corticotropin but not to cortisone treatment. Although it is true that the best temporary improvement in this series was seen in Patient H. S. while he was receiving corticotropin, Patient M. H. received only corticotropin and was but slightly benefited.

One patient with inveterate psoriasis (data on whom are not included in Table 5) was treated twice daily with local applications of 0.5% cortisone ointment for three weeks. All lesions were definitely aggravated. Spies and Stone [11] have reported improvement in two cases of psoriasis following the local application of cortisone ointment.

In this group with collagen diseases, an alarming depression occurred in Patient C. L., who had subacute lupus erythematosus, during her second remission. Three months previously a temporary dramatic remission had followed administration of 3 gm. of cortisone. After the second remission, it was thought advisable to continue giving 100 mg. of cortisone two or three times weekly in the hope of maintaining the remission. Although cooperative, the patient appeared somewhat depressed a week before the last injections, the depression being the only abnormality noted. As this symptom seemed to deepen, therapy was discontinued after a total of 400 mg. of corticotropin and 4.0 gm. of cortisone had been given. Five days later in an acute depression the patient attempted suicide by slashing her wrists. It became necessary to commit her to an institution. When she was observed five months

9. Ragan, C.: Personal communication to the authors.

10. Irons, E. N.; Ayer, J. P.; Brown, R. G., and Armstrong, S. H.: ACTH and Cortisone in Diffuse Collagen Disease and Chronic Dermatoses, J. A. M. A. **145**:861 (March 24) 1951.

11. Spies, T. D., and Stone, R. E.: The Effect of the Local Application of Synthetic Cortisone Acetate on the Lesions of Iritis and Uveitis, of Allergic Dermatitis, and of Psoriasis, South. M. J. **43**:871, 1950.

later, the depression had cleared completely but the lupus was as severe as at the time of her second admission.

In contrast to this, Patient S. S. had frequently spoken of suicide before treatment because her generalized psoriasis and arthritis were so incapacitating but manifested no depression while receiving a total of 34 gm. of cortisone. She showed no consistent improvement in her psoriasis arthropathica and in addition developed moon facies, edema, thrombophlebitis, and an abscess of the buttock.

The only other complications seen were temporary edema in two patients and transient glycosuria in another.

The temporary response and the rebound phenomenon after administration of corticosteroids are shown in the following case:

Illustrative case: H. S., a man aged 47, had extensive psoriasis which had begun at the age of 3 years and had resisted all forms of treatment. For three years, the lesions of the palms and soles had been pustular and arthritic symptoms had been present. On admission he had pustular psoriasis of the palms and soles, with marked involvement of the nails and paronychia. All digits except the left index finger and thumb had become fixed in extreme flexion. The scalp was covered with heaped-up white scales. There was a diffuse erythema of the face and trunk. Large geographic plaques, scaling but not indurated, were present on the legs. A biopsy specimen showed a picture consistent with psoriasis. The patient was given corticotropin, 100 mg. a day, for 16 days. In four hours the eosinophils dropped from 143 to 101 per cubic millimeter. In three days the erythema was less. Pustules continued to appear until the 15th day. By the end of this course the face and trunk were free of scales, though his lesions were defined by slight redness and pigmentation. Pronounced scaling of the scalp and palms remained; the nails were unchanged. There was definite improvement in the arthritic symptoms but no noticeable change in the contractures of the fingers. The erythrocyte sedimentation rate fell from 65 to 30 mm. per hour. Four days after corticotropin therapy (total of 1.6 gm.) was stopped, a shower of pustules appeared on the palms. In the following 18 days he was given seven injections of cortisone, varying from 100 to 300 mg. each. During this period, pustules continued to appear and the lesions on the trunk became more thickened and desquamative than before treatment. Hormone therapy was then abandoned.

Neoplasms: Table 6 emphasizes the transient nature of the improvement seen in lymphoblastomas treated with corticosteroids. The result in Patient M. H. is similar to that reported by Tulipan.[12] The remission obtained was valuable in that it permitted a rest period from irradiation therapy.

One case of acute lymphatic leukemia with extensive skin lesions and severe pruritus responded rapidly to the administration of corticotropin, with a diminution of the white blood cell count from 41,000 to 12,900. As expected, however, the improvement was temporary, and relapse occurred one month after cessation of therapy.

No response was observed in one case of Kaposi's hemorrhagic sarcoma treated with cortisone, although the total dose was admittedly small.

Other Dermatoses (Table 7): No conclusions can be drawn regarding the efficacy of corticosteroids in the one patient with nodular nonsuppurative panniculitis or in the one with total alopecia, as they were inadequately treated. This therapy was of no value in one mentally defective child with acanthosis nigricans who received 1.4 gm. of cortisone in an 18-day period. The drug caused a temporary

12. Tulipan, L.: Failure of ACTH (Adrenocorticotropic Hormone) in the Treatment of a Case of Mycosis Fungoides, J. Invest. Dermat. **15**:349, 1950.

TABLE 6.—*Course in Neoplasms*

Patient	Sex	Age, Yr.	Diagnosis	Duration, Yr.	Location or Extent of Lesions	Drug Used	Treatment: Total Dose, Gm.	Treatment: No. of Days Treated	Result
M. H.	F	56	Mycosis fungoides Diabetes mellitus	2 4	Universal exfoliative dermatitis with plaques on face and trunk	Cortisone	7.0	72	Greatly improved; relapse 3 wk. after therapy; slight increase in glycosuria
A. K.	M	15	Leukemia cutis (acute lymphatic leukemia)	¼	Generalized exfoliative erythroderma with bullae on hands	ACTH	0.560	15	Pruritus diminished in 48 hr.; skin almost clear in 2 wk.; relapse in 1 mo.; died
N. D.	M	46	Kaposi's hemorrhagic sarcoma	5	Widespread hemorrhagic nodules of the skin and mucous membranes	Cortisone	4.0	61	Failure; new lesions appeared; no regression of existing lesions

TABLE 7.—*Course in Other Dermatoses*

Patient	Sex	Age, Yr.	Diagnosis	Duration, Yr.	Location or Extent of Lesions	Drug Used	Treatment: Total Dose, Gm.	Treatment: No. of Days Treated	Result
L. V.	F	53	Nodular nonsuppurative panniculitis	15	Face, neck	Cortisone	0.35	7	Treatment discontinued because of increase in hypertension
J. W.	F	41	Alopecia totalis	7	Scalp	Cortisone	0.4	6	No benefit
I. M.*	F	3	Acanthosis nigricans (benign)	3	Neck, axillas, trunk, extremities	Cortisone	1.425	18	No response
I. S.	M	64	Lichen planus	1	Oral mucosa, genitalia, legs	Cortisone	2.1	16	Improved in 48 hr.; healed in 15 days; recurred 4 mo. later; intercurrent Salmonella montevideo bacteremia
A. M.	F	58	Dermatitis herpetiformis	½	Trunk and extremities	Cortisone	1.05	17	Clear in 6 days; severe recurrence 2 wk. after therapy; temporary glycosuria
R. L.	F	65	Chronic vesicular dermatitis	45 †	Hands	Cortisone	3.3	17	Marked improvement in 3 days; continued on maintenance dose; buttock abscess

* Case reported by Curth, H. O., to be published.
† Intermittently.

remission in one patient with lichen planus and in another with dermatitis herpetiformis. One patient who had been partially invalided by a long-standing dermatitis of the hands with a superimposed x-ray burn showed sustained improvement following administration of 3.3 gm. of cortisone.

The complications in this group of patients during therapy were temporary glycosuria, an increase in preexisting hypertension so that cortisone therapy was discontinued, and a Staphylococcus pyogenes var. aureus abscess at the site of cortisone injection. After cystoscopy and proctoscopy, Patient I. S. acquired Salmonella sp., Type Montevideo bacteremia, and for this reason cortisone treatment was discontinued.

Chronic Dermatitis of Unknown Cause: In Table 8 are reported data on five patients with long-standing chronic dermatitis, two of whom were bedridden. After therapy, improvement was noted in all. In four of the patients this persisted if 100 to 200 mg. of cortisone was given biweekly.

One patient exhibited temporary euphoria and abdominal cramps after treatment with 500 mg. of cortisone. A year later corticotropin was given without recurrence of these symptoms. Patient L. V., who had mild anemia, showed severe aplastic anemia eight weeks after receiving 3.3 gm. of cortisone.

Dramatic response to cortisone therapy is shown in the following case:

Illustrative case: C. R., a man aged 78, was emaciated and bedridden with intolerable pruritus due to an intense universal exfoliative dermatitis of two years' duration. There were pronounced lymphadenopathy and anemia; the presence of lymphoblastoma was excluded by blood studies and biopsy. He had suffered from asthma and allergic reactions to topical therapy.

After four weeks of symptomatic care in the hospital, his anemia improved but his skin and mental condition deteriorated. Two deep lacerations on the forehead resulted from his falling out of bed.

Cortisone, 1.1 gm., was then given during 12 days. The skin appeared less red 12 hours after the first injection, and in three days the infiltration, scaling, and pruritus were greatly diminished. In 12 days pruritus and desquamation had ceased, but the skin remained pink and thickened. The lacerations healed promptly. The patient was up and about. An asymptomatic drop in serum carbon dioxide to 22 mEq. per liter was noted. Five days after the last injection, the pruritus, erythema, and exfoliation recurred. A second course of cortisone therapy, 0.8 gm. given over an eight-day period, caused even more dramatic improvement than the previous one. Maintenance therapy of 100 mg. biweekly for three weeks resulted in a partial relapse which was relieved by a 200-mg. injection followed by administration of 200 mg. biweekly. Remission was maintained with the giving of 200 mg. triweekly for a two months' period after discharge from the hospital.

HISTOPATHOLOGIC STUDIES

Cutaneous biopsy specimens were taken from contiguous sites on the lesions of seven of the patients prior to, during, or after therapy to ascertain whether any noteworthy histologic variations occurred. These included two patients with atopic (allergic) eczema (I. R. and H. F.), one with chronic dermatitis of the exfoliative type (C. R.), one with acute disseminated lupus erythematosus (C. M.), two with psoriasis (S. S. and H. S.), and one with mycosis fungoides (M. V.). All these patients received cortisone with the exception of H. S., who was treated with corticotropin. Sections were prepared with hematoxylin and eosin stain.

Comparison of the sections from both patients with atopic eczema showed a decrease in epidermal edema, acanthosis, and parakeratosis. In addition, the sections

TABLE 8.—*Course in Chronic Dermatitis of Unknown Cause*

Patient	Sex	Age, Yr.	Duration, Yr.	Location of Lesions	Drug Used	Treatment: Total Dose, Gm.	Treatment: No. of Days Treated	Result
C. R.	M	78	2	Universal exfoliative erythroderma	Cortisone	8.0	130	Almost clear; see case report (C. R.)
L. V.	F	55	1	Generalized lichenified and vesicular erythroderma	Cortisone	10.0	135	Pronounced improvement by 5th day; partial relapse 1 wk. after discontinuing treatment; maintenance dosage required; severe aplastic anemia 8 wk. after last cortisone injection
B. C.	F	57	⅔	Widespread exuding scaling dermatitis of face, neck, chest, and arms	Cortisone	3.3	16	Gradual improvement beginning 4th day; maintenance dosage 100 mg. triweekly for 2 mo.; partial relapse
B. K.	F	60	28 *	Pruritic lichenified dermatitis of face, neck, and arms (rheumatoid arthritis)	Cortisone ACTH	0.75 0.30	10 11	Temporary improvement in dermatitis and arthritis; temporary euphoria and abdominal cramps; during second course dermatitis improved; no mental disturbance
W. G.	M	65	1½	Plaques of papulovesicular dermatitis on extremities, trunk, and ears	ACTH Cortisone	0.3 1.4	3 8	Dramatic improvement in 24 hr.; beginning recurrence 4th day after discontinuing therapy; maintenance dose required

* Intermittently.

of the lesions removed from Patient I. R. after 11 days of cortisone therapy (2.2 gm.) disclosed a decrease in leucocytes and fibroblasts within the cutis. Sections from the lesions of H. F. after eight days of cortisone therapy (1.0 gm.) did not show this decrease.

Patient C. R., with chronic exfoliative dermatitis, received 1.2 gm. of cortisone by the 12th day, when the first contrast biopsy specimen was taken. Parakeratosis and leucocytic infiltration of the epidermis had definitely decreased, and keratinization was approaching normality. By the 52nd day, when 4.5 gm. of cortisone had been administered, an increase in parakeratosis was present. At both times there was a decrease in both leucocytes and fibroblasts in the cutis, but this did not appear to be progressive and was quantitatively similar in all the sections removed during therapy.

Three biopsy specimens from the lesions of Patient C. M. with acute lupus erythematosus, who received 5.2 gm. of cortisone, exhibited a definite contrast when compared with the control sections taken prior to therapy. The last one taken on the 43rd day of treatment revealed a decrease in hyperkeratosis, parakeratosis, and edema, while the granular layer was widened. A marked diminution in intensity of the edema in the cutis, as well as in the focal lymphocytic infiltration, had taken place. The connective tissue was more compact, but its collagenous fibers appeared thinner. Fibroblasts were less numerous, and the previous vesicular nuclei were represented by shrunken pyknotic nuclei.

Definite and interesting changes were observed in the patient with psoriasis (S. S.) who received 4.6 gm. of cortisone in 41 days, during which time four biopsies were performed. Parakeratosis regressed remarkedly, and the loose stratum corneum became compact. The granular layer became much more conspicuous and wider. A definite decrease in the inflammatory reaction within the cutis was evident. Another patient (H. S.) was treated with 1.6 gm. of corticotropin during 17 days. The psoriatic lesions had regressed in a manner similar to that in the preceding case, but there was little change in the moderate dermal inflammatory reaction. However, Munro abscesses had disappeared, and there was also a diminution in the number of infiltrating polymorphonuclear leucocytes.

A patient with mycosis fungoides (H. F.) received 7 gm. of cortisone in 72 days. Two biopsy specimens taken before therapy were suggestive but not pathognomonic of mycosis fungoides. However, a biopsy specimen taken 50 days after cessation of cortisone therapy showed greater epidermal reaction, with more keratinization, parakeratosis, acanthosis, edema, and great increase in the width of the granular layer. More interesting, however, was the fact that the dermal infiltration of blastomatous cells had become extreme, and nuclear dust was present in profusion. The microscopic changes in this post-therapy lesion were much more characteristic of mycosis fungoides than were those of lesions excised prior to the administration of cortisone; real tumors had formed in the dermis, in contrast to the more moderate previous infiltrations, and Pautrier's abscesses, which had been present originally, had now disappeared.

Conclusions are somewhat hazardous from so few cases. There does, however, appear to be a favorable influence by either hormone on epithelization. The keratinizing process approaches normal; the stratum corneum becomes more com-

pact; parakeratosis tends to disappear, and keratohyalin granules appear in greater quantity. Inflammatory reaction tends to be repressed, but in this material no definite change was noted in the connective tissue, such as has been observed by others [18] in healing wounds.

COMMENT

Our results emphasize the effectiveness, as well as the shortcomings, of corticotropin and cortisone therapy in the management of various dermatoses. Although there is no evidence that these hormones alter the basic disease processes involved, they often afford the patient prompt symptomatic relief and frequently shorten hospitalization. Perhaps their greatest value is found in the treatment of allergic disorders of limited duration in which the remission obtained may be prolonged enough to cover the natural evolution of the disease. In such cases the favorable response to corticotropin or cortisone can often be realized before any of the undesirable effects become manifest.

Side-effects of hormone therapy were encountered in 27 of the 67 patients included in this report. For the most part, the complications were temporary and mild, but in five instances they were sufficiently severe to require cessation of treatment.

Cerebral effects of hormone therapy were noted in four patients. Two of these showed transient euphoria, one a mild depression, and one a severe depression with schizoid tendencies.

Significant sodium retention or potassium depletion was not observed in any of these patients. Water retention, manifested by edema and weight gain, occurred in four cases, but the symptoms were not severe enough to cause interruption of treatment. Mild glycosuria developed in two patients during hormone therapy, while a third patient with diabetes mellitus and mycosis fungoides tolerated therapy with only slightly augmented insulin requirements. Moon facies occurred in one patient, but other features of Cushing's syndrome, such as hyperpigmentation, acne, and hirsutism, were absent.

Elevation of the blood pressure was noted in two patients, and superficial thrombophlebitis in one. The thrombophlebitis was not associated with abnormality of clotting, bleeding, or prothrombin times. One patient had hematemesis while receiving cortisone, but this was an isolated event and did not recur when hormone therapy was reinstituted in lower dosage. One patient with rheumatoid arthritis and Sjögren's syndrome showed a sharp exacerbation of symptoms during the first five days of therapy. Healing of biopsy sites appeared to progress normally except in one instance in which the incision became secondarily infected. One patient exhibited signs suggestive of acute appendicitis while receiving cortisone. This attack subsided uneventfully after hormone treatment was discontinued, and the relationship of the two remains obscure.

Perhaps the most striking complication seen in these patients was the prevalence of pyogenic infections during hormone therapy. Abscesses at the sites of injection developed in five patients, pustular skin eruptions in five, lymphangitis in three, and parotid gland infection in one. Although superficial pyogenic infections have been noted before during corticosteroid therapy, their frequency has usually not been as high as that encountered in this series.

SUMMARY

Sixty-seven patients with cutaneous eruptions were treated with corticotropin (ACTH) and cortisone. The results may tentatively be summarized as follows:

Beneficial
Drug eruptions
Urticaria
(not due to light)
Dermatitis venenata

Of Temporary Benefit	Probably of No Benefit
Lupus erythematosus	Dermatomyositis
Lichen planus	Psoriasis arthropathica
Dermatitis herpetiformis	Sjögren's syndrome (keratoconjunctivitis sicca)
Chronic dermatitis of unknown cause	Solar urticaria
Leukemia cutis	Kaposi's sarcoma
Mycosis fungoides	Acanthosis nigricans
Atopic (allergic) eczema	Nodular nonsuppurative panniculitis
	Total alopecia

Complications were noted in 27 patients. In one patient a serious depression occurred. The number of infections seemed disproportionately high. Other complications were temporary.

As a certain degree of hyperadrenalism occurs after administration of corticotropin or cortisone, it seems advisable to have patients under continuous observation when treatment is prolonged.

Dr. Paul Gross gave permission for publication of two cases.

ACUTE FORMS OF PEMPHIGUS

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IN A DISCUSSION of acute pemphigus we must be careful to distinguish between the rare form designated as acute febrile grave pemphigus (so-called pemphigus acutus) and the acute forms or phases of pemphigus vulgaris. It is the latter condition with which we are chiefly concerned here, but the former will be discussed briefly.

ACUTE FEBRILE GRAVE PEMPHIGUS

Acute febrile grave pemphigus is characterized by a peracute bullous eruption, accompanied by marked symptoms of a severe septic state, and a fatal termination. The onset is sudden and the eruption extensive, beginning as large bullae that often become hemorrhagic. The bullae grow rapidly and soon burst, leaving large, moist or bloody denuded areas that become confluent, resembling in appearance an extensive burn. A high septic fever, chills, and often diarrhea accompany the cutaneous eruption. The patient's course is rapidly downhill, and death ensues in one to three weeks.

The condition is extremely rare and the only significant etiologic observation recorded is that a number of such cases have been seen in butchers, meat handlers, and farmers. Cases have also been reported following surgical operation upon patients in whom severe sepsis existed prior to operation. Authorities have disagreed in their concept of this acute bullous disease. Some believe it to be a sepsis not in any way connected with pemphigus vulgaris, while others maintain still that it is a very severe, rapidly fatal form connected with true pemphigus. I believe that they are distinct clinical entities. I have seen only two cases which may be classified as the acute febrile grave form, and none in recent years. It would be interesting to learn what effect the antibiotics would have on the outcome of the disease.

Albin Proppe [1] of Dusseldorf recently reviewed the literature and attributed the eruption to a manifestation of the Sanarelli-Schwartzman phenomenon. He based this deduction on the fact that, in the case reports which he concluded were true examples of acute febrile grave pemphigus, there had been a history of previously infected skin or a vocation from which it might be inferred that the infection occurred in a prepared or sensitized skin. If a preexisting pyoderma or the presence of patho-

Read at the meeting of the American Academy of Dermatology and Syphilology, Dec. 7, 1950.

From the Division of Dermatology, University of Minnesota (H. E. Michelson, M.D., Director).

1. Proppe, A.: Pemphigus Acutus Febrillis Gravis, Arch. Dermat. & Syph. **187**:364 (Nov.) 1948.

genic organisms on the hands or elsewhere could be proved in every such case, the pathogenesis of acute febrile pemphigus might be identified with the Sanarelli-Schwartzman phenomenon.

ACUTE PEMPHIGUS VULGARIS

It is difficult to determine exactly what is meant by the term acute pemphigus vulgaris. Does it merely describe pemphigus vulgaris of sudden onset, or should the term be reserved for cases in which death occurs in a few weeks? In many patients

Fig. 1.—Pemphigus acutus febrilis gravis.

pemphigus vulgaris appears with a sudden, severe, widespread eruption which, after passing through a severe initial stage, becomes much less severe, either because therapy was effective or because of the natural history of the disease. At times the eruption may even disappear completely, but it almost always recurs.

I do not believe that it is possible at the onset to determine whether the disease will be acute throughout its course or whether, for various reasons, the patient will improve enough to have a protracted course or even to be free of visible manifestations of the disease. There are, in addition to the character of the eruption, a few signs, symptoms, and laboratory procedures which help in determining the severity in a given case.

Pemphigus vulgaris may begin insidiously with only one or two lesions which sometimes have been interpreted as initial lesions. Such an initial lesion is often nondescript, frequently appears on the scalp, and is characterized by persistent oozing and crusting. It is often diagnosed as impetigo, pyoderma, or a plaque of seborrheic eczema. However, its lack of response to medication that would normally influence such lesions favorably should arouse suspicion, and the patient should be watched for the appearance of further lesions. Pemphigus vulgaris may also begin with a rather widely spread, polymorphous eruption which when first seen appears to be benign, involving parts of the body not looked upon as areas of predilection for pemphigus; bullae are not at first apparent. The eruption in such a case resembles fixed, severe, urticarial wheals which may have purpuric spots. I have seen these eruptions on the hands, even on the palms and on the trunk. Their evolution is fairly rapid, however, and soon either recognizable bullae develop in what may be known as the pemphigus areas, i. e., the axillae, the inguinal regions, the umbilicus,

Fig. 2.—Initial eruption in patient who later manifested severe pemphigus vulgaris and died in four months.

the intergluteal fold, and the mouth or other mucous membranes, or the initial eruption becomes denuded in its center, and the epidermis at the periphery is undermined and becomes scalloped, and one realizes that the lesions are, in fact, disguised bullae. In my experience, it is a rarity to see pemphigus vulgaris begin as bullae, filled with clear fluid, erupting on an unaltered skin.

It must be emphasized that pemphigus vulgaris may begin as an eruption which even a dermatologist with a vast experience in pemphigus cannot diagnose at its inception. I believe it can be said that pemphigus vulgaris may often not be suspected at its onset, but, conversely, other conditions are rarely diagnosed as pemphigus. For this reason pemphigus vulgaris should always be considered as a possibility, especially in cases of odd eruptions which denude easily.

As previously stated, it is difficult to define acute pemphigus vulgaris, and it should be emphasized that the severity of the disease is more important than the time element. The course may be prolonged for months, and still the disease may be con-

sidered acute. On the other hand, the chronic form of pemphigus vulgaris may be diagnosed fairly early in the course of the disease because of symptoms which are recognized as features of the torpid variety. I look upon pemphigus vulgaris as a condition which may begin either insidiously or violently but which soon has a widespread eruption that may or may not involve the mucous membranes. Constitutional symptoms of a severe infection become evident shortly after the eruption is established and persist throughout the course of the acute form of the disease. By acuity we really mean severity, and this must be judged by evaluation of the condition of the patient. Some degree of remission may occur, but in acute pemphigus vulgaris there is never complete disappearance of the lesions and the symptoms. If the disease begins with a severe initial eruption, and if in the course of time the skin becomes partially free from eruption and the patient has no systemic symptoms, the condition may no longer be looked upon as acute pemphigus vulgaris but must be diagnosed as the chronic form. This is quite a common occurrence.

To summarize, acute pemphigus vulgaris is diagnosed as such because of its severity and persistence. Obviously, an early fatal termination establishes the condition as an acute one. Chronic pemphigus vulgaris may have periods of acuity, but remissions of long duration place it in the chronic group. The natural history of the course in pemphigus vulgaris is unpredictable and capricious. Sudden changes are to be expected; early decisions concerning type and prognosis are therefore unwise.

I believe that pemphigus vegetans and pemphigus foliaceus should be looked upon as particular forms of the general disease under discussion. However, if an eruption that has been diagnosed as pemphigus vulgaris becomes localized and exuberant in the areas for which pemphigus vegetans has predilection, if the patient's constitutional symptoms subside or disappear, and if his course is protracted, the diagnosis becomes pemphigus vegetans. If acute phases occur, new outbursts of the vulgaris type of lesion may be expected. On the other hand, pemphigus vegetans may begin acutely, remain the vegetating type throughout its course, and end fatally in a comparatively short time. Therefore, an acute form of pemphigus vegetans must be recognized.

Pemphigus foliaceus, too, may begin as pemphigus vulgaris, either slowly or by a rapid spread to all parts of the body, but I have not seen an acute form of pemphigus foliaceus which began as a generalized eruption, quickly assumed the exfoliant character of pemphigus foliaceus, and terminated in a matter of weeks. In general, pemphigus foliaceus belongs in the classification of the chronic forms.

The differential diagnosis of acute pemphigus is difficult. Since the decision must be made arbitrarily upon the morphology, the margin of error is large, and disagreement between clinicians is to be expected. The tendency is to diagnose any bullous eruption as one of the lesser members of the pemphigus group, for it is wishful thinking to believe the condition is a dermatitis medicamentosa, erythema multiforme, or even dermatitis herpetiformis. It must be borne in mind that most cases of acute pemphigus do not begin with flaccid bullae appearing on a normal skin. There is usually a distinct erythematous area in which the first indicator of pemphigus may be small vesicles, purpuric or hemorrhagic spots, or merely denudation. The bullae may form in the center or at the periphery of such an area and appear to come up through the erythema as though it were a disguise. It is very important,

however, not to diagnose pemphigus at the first examination, regardless of the severity of the eruption. A few days of observation, during which corroborative evidence is accumulated, is the wisest course. What other evidence may one seek? Rather than reiterate well-known principles of the differential diagnosis of bullous eruptions, I shall list some observations made on our patients and some of the laboratory and other findings which we have found of value in diagnosing pemphigus vulgaris.

Age.—The majority of our patients were over 50 years old, and a considerable number were in the 70-to-80-year group.

Race.—In our material there were few Jewish patients. In 27 necropsies done at the University of Minnesota upon patients dying of pemphigus, there were no Jewish patients, and in 33 patients observed in the past five years, only two were Jews.

Sex.—In our series there were more men than women, but the preponderance was not significant.

Occupation.—Of the 33 patients mentioned, all but 2 belonged to what might be called the laboring class. Many were farmers. It is my impression that pemphigus is much more common in hospital and clinic practice; however, we have made no statistical study to prove such a contention.

Fever.—It has been our experience that almost all patients with pemphigus have elevations of temperature which are, to be sure, variable, but which are persistent. In severely ill patients, the temperature elevation is of the septic type and may be very high. The temperature charts of patients with acute pemphigus vulgaris and acute lupus erythematosus are very similar. The two conditions have much in common.

Weight Loss.—Weight loss is the rule in established pemphigus. However, there may be extensive, cutaneous involvement, and yet, until systemic symptoms become severe, the weight remains stationary.

Urinary Suppression.—Kidney impairment, in contrast to that found in acute lupus erythematosus, must be rare in pemphigus. Robert [2] reported a case of severe pemphigus with retention of urine. The diuretic, "deriphyllin" (a theophyllin preparation), was given with good results; there was a return to normal of the proteins of the blood and the chemical constituents of the urine, and the skin lesions healed. Diuresis certainly deserves a trial in a group of pemphigus patients.

Blood Findings.—The cellular elements of the blood did not show any startling changes, nor did marrow studies reveal significant findings. All the patients had some degree of eosinophilia. The presence or absence of eosinophilia we believe is of little or no value in a differential diagnosis between pemphigus and dermatitis herpetiformis. Blood urea nitrogen was found to be elevated in a few of our patients.

Hocker [3] examined the blood in 40 patients with pemphigus. He considers a marked diminution of hemoglobin contact and the number of erythrocytes to indicate a poor prognosis and states that if a patient with these symptoms is not benefited by whole-blood transfusions, his case may be judged to be of the malignant, early-lethal

2. Robert, P.: Zur Pathogenese und Therapie des Pemphigus vulgaris, Dermatologica **98**:257, 1949.

3. Hocker, H.: Die Kennziechnung der remissionsfähigen und der malignen Verlaufsform des Pemphigus chronicus nach dem Blutbild, Arch. Dermat. u. Syph. **187**:13, 1948.

type. Our observations entirely uphold this view, but we have seen improvement when blood plasma was given.

Histology.—We have done biopsies of all of our patients with pemphigus. Choosing an intact blister and freezing it with an ethyl chloride spray, we have been able to excise the unruptured lesion. It is our conviction that pemphigus cannot be diagnosed microscopically, although some information is gained. Other bullous diseases, even the early bullous lesions of impetigo, have a great similarity to it. Some lesions of dermatitis herpetiformis have distinguishing features. Percival [4] has reported extensive pathologic studies on bullae. His work deserves careful perusal. Cytologic examination of direct smears from an open lesion, if the smears have been properly fixed and stained, may reveal epithelial cells of an acantholytic type which Tzanck [5] and others believe to be diagnostically characteristic. My experience with this method is limited, but as Zoon and Mali [6] aptly state, "The interpretation of epidermal cell morphology as a diagnostic method (Tzanck) appears to us, except perhaps in very skilled hands, a ticklish affair."

Porphyrins.—In eight patients we found a rather marked increase in the excretion of coproporphyrin, but we found no evidence of severe liver damage.

Proteinemia.—We have found depressed serum protein during the severe phases of the disease, with an increase of gamma globulin. The serum albumin dropped decidedly and was the indication for amino acid feedings, often with gratifying results.

Sedimentation Rate.—This was increased, ranging from 60 to 120 mm. in 60 minutes. We have examined our pemphigus patients with every means at the command of the medical staff of the University of Minnesota Hospitals, but we have not found any unexpected or new abnormalities.

Grais [7] succeeded in producing typical bullae in patient with advanced pemphigus by intradermal injections of hyaluronidase. Glick and Grais [8] found no hyaluronidase present in the bullous fluid of patients with pemphigus. They did, however, find that the hyaluronidase-inhibitor level of the serum is greatly increased in pemphigus.

Treatment.—We believe that we have made some advances in the treatment of the pemphigus patients. We are certain that concentrated hospital nursing care will save and, I may say cautiously, cure some of the patients. We insist that the patient be hospitalized immediately when the diagnosis is made or even suspected. This is done to enable the patient to marshal whatever defenses he possesses. The nutrition and the comfort of the patient is maintained at the highest level possible. The integument is kept scrupulously clean by bathing or spraying, and pressure bandages are used. The lesions are covered with petrolatum and gauze dressings, then elastic bandages are applied to the extremities, and muslin binders are pinned snugly around

4. Percival, G. H., and Hannay, P. W.: Observations on Structure and Formation of Bullae, Brit. J. Dermat. **61**:41, 1949.

5. Tzanck, A.: Le cytodiagnostic immédiat en dermatologie, Ann. dermat. et syph. **8**:205, 1948.

6. Zoon, J. J., and Mali, J. W. H.: Remarks on Cell-Diagnostics in Normal and Some Pathological Conditions of the Skin, Dermatologica **101**:145, 1950.

7. Grais, M. L.: Production of Bullae in Pemphigus with Hyaluronidase, J. Invest. Dermat. **13**:221, 1949.

8. Glick, D., and Grais, M. L.: Concerning the Alleged Occurrence of Hyaluronidase in Skin, Arch. Biochem. **18**:511, 1948.

the trunk and chest. A variety of high-protein preparations have been tried and have been of decided help in reestablishing osmotic pressure. If, under such a regimen, the patient improves steadily, we need not resort to any drugs, such as arsenic or surinam sodium.

If the patient's course is downward, blood transfusions and antibiotic therapy, penicillin first, then aureomycin, are administered. If the patient does not respond, cortisone, followed by corticotropin (ACTH) have been tried. At the present time, we believe that none of these procedures or drugs may be determined to be the treatment of choice. Each pemphigus patient may respond differently to the treatments administered. His inherent defensive and recuperative powers seem to be the determining factor in the outcome. These may be helped in one patient by one remedy and in another by a different procedure. The order of trial will depend upon the experiences of the staff in charge of the patient. At present there is no specific therapy.

SUMMARY

The conditions which make up the pemphigus group are varied in their manifestations, their severity, and the course which each pursues. Despite the antiquity of the disease and the great efforts that have been made to find its cause and its pathogenesis, little of real value has been learned.

Pemphigus belongs to dermatology. It has not been the problem of any other branch of medicine, and it is to be hoped that by careful classification, study, and research dermatologists will be the leaders in solving the problem of this terrifying disease.

Medical Arts Bldg.

CHRONIC PEMPHIGUS VULGARIS

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IT IS DIFFICULT, as Michelson [1] states, to draw a sharp line of distinction between acute and chronic pemphigus vulgaris, and consequently there may be some overlapping in our presentations.

As I have looked over some of the literature dealing with pemphigus, I have been struck with the fact that, while much investigative work has been done, one finds a notable diversity of opinion with regard to the diagnosis, cause, and therapy of this disorder.

CAUSE

Among the various ideas as to the cause we find infection, disturbance of the glands of internal secretion, toxic agents, and a neuropathologic condition recorded. With regard to infectious agents, it is difficult to discover confirmation by other workers of the findings of those who believe that they have discovered significant organisms. Eberson,[2] in 1923, reported that he had found in the blood of seven different patients, and in the blister fluid of one of these, a Gram-positive, anaerobic, nonmotile organism, oval or coccoid in form, resembling in some respects a Streptobacillus. He stated that the organism was pathogenic for guinea pigs and rabbits. He felt that it possessed definite toxic properties, and he was able to produce suggestive lesions with recently isolated strains. He was also able to reisolate the germ from the blood of infected animals. Welsh,[3] in 1934, presented evidence pointing toward a Streptococcus as the possible pathogenic agent and showed that the organism was virulent for five species of animals; and he was able to produce lesions consistent with pemphigus in a fair number of subjects. In 1946, Welsh [4] reported a more extensive study, and in a total of 152 pure cultures of material taken from various sources in 23 patients with pemphigus he found a pleomorphic Streptococcus with a characteristic cataphoretic mobility curve. The organism was virulent for laboratory animals, and in a few instances lesions resembling pemphigus were produced in these animals. Welsh suggested that pemphigus is a streptococcal disease in which the organism is present in the mucosa and in foci of infection, from which

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1. Michelson, H. E.: Acute Forms of Pemphigus, A. M. A. Arch. Dermat. & Syph., this issue, p. 422.

2. Eberson, F.: Studies of Etiology of Pemphigus: I. Bacteriologic Findings in a Group of Cases of Pemphigus, Arch. Dermat. & Syph. **8**:204 (Aug.) 1923.

3. Welsh, A. L.: Specificity of a Streptococcus Isolated from Patients with Pemphigus, Arch. Dermat. & Syph. **30**:611 (Nov.) 1934.

4. Welsh, A. L.: J. Invest. Dermat. **7**:7, 1946.

dissemination into the blood stream occurs. For him, the skin lesions result when the organism or its products reach the sensitized skin. Curtis and Topp,[5] however, reported in 1947 that they attempted to duplicate this work, and in 32 blood cultures in nine patients recovered no streptococci and obtained negative results from intraspinal and intracerebral inoculation with the blood of patients with pemphigus.

Work suggesting a virus as the cause of the disease has been reported by Landford,[6] Urbach and Wolfram,[7] Grace,[8] and others. Urbach and Wolfram in 1936 concluded that their studies pointed to a filtrable virus as the cause of pemphigus, and they felt that dermatitis herpetiformis was caused by the same virus. Grace and Suskind [8] in 1939 recorded isolation of an agent transmissible to mice (a nonbacterial agent), and in 1946 Grace [9] reported a study which he felt warranted the conclusion that a virus, whose characteristics he described, is the etiologic agent of pemphigus. Markham and Engman,[10] however, in 1940 reported experiments designed to demonstrate the presence of a filtrable virus in the blister fluid of lesions of pemphigus, but their results were entirely negative, and they felt that there was insufficient evidence to justify the acceptance of the virus origin. Behcet [11] in 1943 attempted to duplicate the work of Lindenberg, which pointed toward a viral agent, but was unable to confirm those findings. Cambel [12] in 1943, in autopsies of three patients with pemphigus, found signs of an infectious toxic reaction, but could demonstrate no virus upon staining. In 1947, Grace [13] presented studies of the blood cells in patients with pemphigus and felt that the findings indicated a virus and not a pyogenic agent. He stated that the blood picture in pemphigus is identical with that of a generalized infection, but that in pemphigus the increased number of white cells does not arise from the polymorphonuclear series but results from an increase in the total number of each type of leucocyte present normally in circulating blood. Travassos and Hadler [14] in 1947, studying Grace's work, reported the finding in a patient of some elementary bodies, although they do not feel that it can be stated that the virus was the cause of the pemphigus, as it may have been only secondarily associated. Mezzadra and Rabito [15] in 1949 carried out a series of experiments with the blood and bullous fluid of patients with pemphigus and dermatitis herpetiformis and could not support the theory of virus origin.

Regarding disturbances of metabolism, a considerable literature has been produced. Brochner-Mortensen [16] in 1938 called attention to the tendency to edema

5. Curtis, A. C., and Topp, J. M.: J. Invest. Dermat. **9**:151, 1947.

6. Landford, J. A.: South. Med. J. **21**:35, 1928.

7. Urbach, E., and Wolfram, S.: The Virus of Pemphigus and Dermatitis Herpetiformis, Arch. Dermat. & Syph. **33**:788 (May) 1936.

8. Grace, A. W., and Suskind, F. H.: J. Invest. Dermat. **2**:1, 1939.

9. Grace, A. W., and Suskind, F. H.: Bull. New York Acad. Med. **22**:480, 1946.

10. Markham, F. S., and Engman, M. F., Jr.: Inquiry into the Cause of Pemphigus: Is It a Virus Disease? Arch. Dermat. & Syph. **41**:78 (Feb.) 1940.

11. Behcet, H., and others: Dermatologica **87**:113, 1943.

12. Cambel, P.: Dermatologica **87**:127, 1943.

13. Grace, A. W.: Pemphigus Vulgaris: Study of Blood Picture, Arch. Dermat. & Syph. **55**:772 (June) 1947.

14. Travassos, J., and Hadler, W. A.: Bruxelles-méd. **27**:1983, 1947.

15. Mezzadra, G., and Rabito, C.: Gior. ital. dermat. e sif **90**:106, 1949.

16. Brochner-Mortensen: Acta med. scandinav. **97**:329, 1938.

seen in pemphigus, and recorded the notable reduction in the serum-protein content, especially the albumin fraction. This change, noted by others, is attributed to the loss of fluid through the bullae and the oozing denuded areas. In 1906, Cassaët and Micheleau [17] suggested a disturbance in the salt-water metabolism, often seen in adrenal insufficiency, as a finding in pemphigus; and Talbott and Coombs [18] in 1940 were of the opinion that pemphigus was intimately associated with one or more disturbances of metabolism, as such persons show an increase in the volume of plasma, blood, and interstitial fluid. Talbott and Lever,[19] also in 1940, reported a striking reduction of serum sodium and calcium; and as further evidence of an acid-base imbalance, there was an increase in the serum potassium and an increase in the nonprotein nitrogen. Goldzieher [20] in 1945 studied the adrenal glands in six patients at autopsy and found similar changes in all. Depending on the duration of the disease, the changes varied from acute degeneration and inflammation, necrobiosis, and depletion of lipids to nodular hyperplasia and fibrosis, changes which may account for the changes pointed out by Talbott and his associates. In a later report (1946), Goldzieher [21] recorded another case in which the patient had a congenital malformation of the left adrenal gland, while the gland on the right side had been destroyed by a thrombosis of not-too-recent date. In very recent times the use and, at times, good effects of corticotropin (ACTH) and cortisone and other cortical extracts have served to place further emphasis upon consideration of the endocrine aspects of this disease. Florian and Vertes [22] in 1948 found that in pemphigus the serum potassium was raised on an average by 20% and the cholesterol by 10%. Lever and Talbott [23] felt that these changes in water and salt metabolism, which are not evident in acute pemphigus, might be of aid in differentiating this type from the chronic form.

Barnard [24] in 1947 reported the case of a patient with pemphigus with estropenia (diminution in blood cholesterase and erythrophthisis) at autopsy. He suggested that pemphigus may be due to erythroid marrow depression, failure of cholesterinase synthesis, and cholinergic intoxication.

Macht and Ostro [25] in 1947 added a diagnostic test to supplement the Pels-Macht test. They found that if pemphigus serum exposed to x-rays is detoxified, while the air-exposed comparable specimen remains toxic, the diagnosis of pemphigus is established. Macht and Insley [26] felt that the skin and mucous-membrane lesions of pemphigus are only the external manifestations of a severe toxemia, and that this is not due to a bacterial infection.

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17. Cassaët, E., and Micheleau, E.: Arch. gén. méd. **1**:129, 1906.

18. Talbott, J. H., and Coombs, F. S.: Pemphigus: Experimental Studies on 34 Patients, Arch. Dermat. & Syph. **41**:359 (Feb.) 1940.

19. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: J. Invest. Dermat. **3**:31, 1940.

20. Goldzieher, J. W.: Adrenal Glands in Pemphigus Vulgaris: Report of 6 Autopsies and Review of Literature, Arch. Dermat. & Syph. **52**:369 (Nov.-Dec.) 1945.

21. Goldzieher, J. W.: Adrenal Glands in Pemphigus Vulgaris, Arch. Dermat. & Syph **53**:42 (Jan.) 1946.

22. Florian, and Vertes: Ann. dermat. et syph. **4**:342, 1948.

23. Lever, W. F., and Talbott, J. H.: New England J. Med. **231**:44, 1944.

24. Barnard, R. D.: Urol. & Cutan. Rev. **51**:586, 1947.

25. Macht, D. I., and Ostro, M.: J. Invest. Dermat. **8**:171, 1947.

26. Macht, D. I., and Insley, M. C.: Urol. & Cutan. Rev. **51**:651, 1947.

The question of family incidence has its etiologic implications. Greenbaum [27] has recorded cases occurring in father and son, in sisters, and in husband and wife. Feldman [28] has reported the disease in two brothers, and Kaposi [29] and Morris have also reported multiple cases in a family. Gellis and Glass [30] stated that in their series several cases suggested a familial contact factor in the causation of the disease.

DIAGNOSIS

I wish to emphasize here something which Michelson [1] has pointed out, namely, the impossibility of making a definite diagnosis at the outset, and, indeed, ever, in some cases. One cannot peruse many society transactions without being intensely aware of the frequency with which opinion is divided among a number of competent observers, when a case is presented, as to whether the patient has pemphigus or dermatitis herpetiformis, and less often, whether pemphigus or erythema bullosum. As Brain [31] recently stated

> The pemphigoid group includes the several varieties of pemphigus vulgaris and dermatitis herpetiformis. Although it may be possible to make one diagnosis or the other, there are many cases which have to be labelled simply as bullous eruptions and observed over a period of time until the characteristic clinical picture is developed. Many observers have seen cases which at first presented features of dermatitis herpetiformis, and later settled down into a true pemphigus.

A typical quotation from a case presentation is "When I examined this patient the first time, I thought he had pemphigus; the next time he presented gyrate erythematous patches, so I changed my diagnosis to dermatitis herpetiformis, or possibly erythema multiforme." Or, as Nekam Jr., and Florian [32] phrase it, "Patients with dermatitis herpetiformis seldom show all the characteristics described by Duhring; a certain number of cases of both diseases show transition from one to the other, starting with the symptoms of dermatitis herpetiformis and developing later as pemphigus." MacLeod,[33] who in 1915 felt that pemphigus and dermatitis herpetiformis should in the present state of knowledge be considered as two different diseases, then stated, "Cases do arise which are exceedingly difficult to place, and may be regarded as almost transitional between the two." Another quotation from Society transactions is as follows:

> I can recall case after case presented in these meetings at which the diagnosis was not settled until years later. I presented a case as one of pemphigus vulgaris with excellent photographs and proper legends. Later, after the patient had a complete remission, the case was presented with equally good photographs as dermatitis herpetiformis.

In recent years, I have become increasingly aware of the necessity of maintaining this viewpoint in certain situations, and I have been particularly impressed with

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27. Greenbaum, S. S.: Cases of Familial and of Congenital Pemphigus Vulgaris, Arch. Dermat. & Syph. **41**:1073 (June) 1940; Pemphigus Vulgaris in Mother and Daughter, ibid. **46**:571 (Oct.) 1942.

28. Feldman, S.: Pemphigus in Brothers, Arch. Dermat. & Syph. **33**:730 (April) 1936.

29. Kaposi: Arch. Dermat. u. Syph. **34**:92, 1896.

30. Gellis, S., and Glass, F. A.: Pemphigus: Survey of 170 Patients Admitted to Bellevue Hospital from 1911 to 1941, Arch. Dermat. & Syph. **44**:321 (Sept.) 1941.

31. Brain, R. T.: Medicine Illustrated **4**:17, 1950.

32. Nekam, Jr., and Florian, in Editions of University Clinics for Skin and Venereal Diseases, Budapest, 1946, Vol. 1, p. 152.

33. MacLeod, J. M. H.: Brit. J. Dermat. **27**:201, 1915.

the fact that many of the differential points which have been emphasized over the years are often far from reliable.

In the past several years I have seen several patients whose cases have illustrated the difficulty of making a differential diagnosis between pemphigus, erythema bullosum, and dermatitis herpetiformis. Without going into detail, I would like to refer to two of these cases.

The first case was that of a woman, 66 years old, in whom a bullous eruption had developed several weeks before she entered the hospital. At the time of entry to the hospital, she had a generalized bullous eruption accompanied with oral lesions, and the picture seemed to be typically that of pemphigus vulgaris. Treatment with acetarsone was instituted, but after three days of this medication the eruption had become much more extensive and had changed its character completely. There were now present upon the trunk and extremities a large number of lesions which were typically the herpes iris type seen in erythema multiforme. Because of the presence of these lesions, it was felt that the original diagnosis had been incorrect and that the patient had actually had erythema bullosum from the outset. She remained in the hospital, and, with no specific treatment but with the employment of various supportive measures, she showed improvement to the point that the eruption had nearly disappeared. There was an exacerbation, however, and with this relapse the picture again changed, the distribution now being that of dermatitis herpetiformis: The lesions were strikingly grouped and multiforme, and there was intense pruritus, a symptom which had troubled the patient but little previously. At this period we felt that had we been seeing the patient for the first time, we would have made an unequivocal diagnosis of dermatitis herpetiformis. This episode was followed by a gradual clearing of the eruption to the point that the patient was permitted to go home. She returned to the hospital within a short time, however, on this occasion again presenting the original picture, namely, that of pemphigus vulgaris. She died three and one-half months after we first saw her, death being due to pericarditis.

The second patient was a man whom I saw through the courtesy of Dr. O. S. Ormsby and Dr. M. Ebert while they were absent from the city. In this case the eruption had begun in the middle of August with a vesiculobullous dermatitis which had appeared first upon the wrists and then gradually extended to involve the trunk, extremities, and neck. In addition to the vesicular eruption, the patient presented many lesions of a maculopapular type, some of these becoming confluent to form large erythematous patches in the regions of the wrists and elbows. The mucous membranes were not involved. There was edema of the hands and legs. The patient was admitted to the hospital on Sept. 2, 1947, with the diagnosis of erythema bullosum having been made by Dr. Ormsby and Dr. Ebert. When I first saw the patient a week later, there were present upon the trunk a large number of typical herpes-iris lesions of deep-red color. The upper arms showed a diffuse erythema of intense degree. Two days later the patient showed a similar diffuse erythema involving the outer aspects of the right thigh, with some herpes iris lesions about the margins. Within a short time many fresh bullae appeared upon this erythematous base. Within the next two weeks patches of intense erythema developed from time to time, with superimposed bullae upon various parts of the trunk and extremities,

while on other parts large annular lesions of erythema-multiforme type appeared. During all this time the patient presented no lesions of the mucous membranes, and no Nikolsky's sign was demonstrable. On Oct. 1 some erosions of the palate developed, and bullae were present upon the lower lip. A week later the patient presented typical bullous lesions of the mucous membranes and showed many erosive lesions in the inguinocrural region, and at this time Nikolsky's sign was demonstrable. It was apparent then that the diagnosis was pemphigus, although it was still difficult to reconcile with this diagnosis the presence of the extensive areas of erythema and the groups of herpes iris and annular lesions which had developed from time to time. After the onset of the mucous-membrane lesions, the patient's condition became suddenly worse, and he died on Nov. 28, 1947.

It is interesting to note statements by various observers, when speaking extemporaneously at society meetings. Wile [34] said

> I wonder if other members of the Society feel as I do with regard to diagnostic criteria. It seems to me that either this disease is changing or else the criteria have been far too rigid. As I look back, pemphigus seemed a disease very easy to diagnose; bullae were present, which usually arose from a nonerythematous base and were usually associated with lesions in the mouth. Lately I have come to the opinion that I regard every patient past 50 with bullous lesions as having potential pemphigus.

He then described a case similar to one I described today, with typical dermatitis herpetiformis at the start and later the appearance of pemphigus; and another in which the disorder appeared to be erythema multiforme at the outset, then became typically pemphigus.

At the same meeting, O'Leary [35] said that he had the same viewpoint and wondered whether dermatitis herpetiformis was becoming more malignant or pemphigus more benign. Two years later O'Leary [36] reiterated the above statement and said

> For several years I have seen with increasing frequency patients who present bullous lesions of the mucous membranes, with bullous cutaneous eruptions developing later and with the disease settling down in a short time to follow a prolonged, benign course. At present I consider these patients to have dermatitis herpetiformis, because of the benignity of the disease, in contrast to the virulence of pemphigus. If this is so, lesions on the mucous membranes are not now uncommon in dermatitis herpetiformis. In any event, I am having more trouble in differentiating these two diseases.

This situation is not new, of course, as evidenced by a paper by Cranston Low [37] in 1909. He described a case in which the disorder began as dermatitis herpetiformis, but later the appearance changed entirely, and the eruption took on the character of pemphigus foliaceus; and then again later, upon improving, it reverted to the picture of dermatitis herpetiformis. This tendency for dermatitis herpetiformis to eventuate in pemphigus foliaceus had been described previously by Biddle,

34. Wile, U. J., in discussion on Rattner, H., and Cornbleet, T.: Case for Diagnosis (Bullous Eruption), Arch. Dermat. & Syph. **43**:1062 (June) 1941.

35. O'Leary, P. A., in discussion on Rattner, H., and Cornbleet, T.: Case for Diagnosis (Bullous Eruption), Arch. Dermat. & Syph. **43**:1062 (June) 1941.

36. O'Leary, P. A., in discussion on Oliver, E. A.: Pemphigus Vulgaris, Arch. Dermat. & Syph. **47**:452 (March) 1943.

37. Low, R. C.: Brit. J. Dermat. **21**:101, 1909.

Brocq, Hallopeau and Fournier, Hallopeau and Jousset, Mracek, Besnier, and Klotz. Hallopeau and Jousset [38] stated

> Pemphigus foliaceus may develop secondarily to dermatitis herpetiformis from which it is a transformation. This transition may be attributed to a change in the reaction of the patient to the disease or to a change in the quantity or quality of the pathogenic toxins producing it.

Recently, Dr. E. A. Oliver [39] had a patient with a typical picture of dermatitis herpetiformis. She was treated with sulfapyridine, but a picture of pemphigus foliaceus developed, and she died within a short time.

What then of the criteria usually cited as valuable in the differential diagnosis of these several bullous conditions?

1. Bullous lesions: In pemphigus the onset with bullous lesions has been emphasized. It is true that this may occur, but it is equally apparent that in many instances, as Michelson has stated, the lesions may arise on a primary inflammatory base.

2. Itching: The presence of itching in dermatitis herpetiformis and its absence in pemphigus has been cited as a criterion. Numerous observers, however, have described pruritus, sometimes intense, in typical cases of pemphigus. For some, the term pemphigus pruriginosus is synonymous with dermatitis herpetiformis, but others, such as Oppenheim, used it as a designation for pemphigus vulgaris accompanied by itching. Hollander [40] in 1941 stated, "Our patient, who unquestionably has pemphigus, also had itching during his early and secondary stages, which symptom, I believe, is not stressed in texts." Gellis and Glass [30] stated that in pemphigus, among 170 patients itching was found to be a common symptom, so far as the records were concerned. They commented, however, that this was not the experience of most dermatologists, and they commented on the uniform absence of excoriations as confirming this opinion.

3. Eosinophilia: To quote Mitchell,[41] "In dermatitis herpetiformis, eosinophilia may be entirely lacking both in the blood and in the contents of the vesicles."

4. Mucous membrane involvement: It is unquestionably true that the mucous membranes are much more frequently involved in pemphigus than in dermatitis herpetiformis, but you will recall the comment by O'Leary cited above, and MacLeod [42] in 1914 studied 100 patients with dermatitis herpetiformis and found the buccal mucosa involved in 10, the genital mucous membranes in 11, and the vulvae in 1. He also noted, as have others, that the conjunctivae may be involved in dermatitis herpetiformis, leading to essential shrinking and blindness, as in ocular pemphigus.

5. Nikolsky's sign: In the original description of this sign Nikolsky stated that in pemphigus foliaceus when the stratum corneum is pulled it can be stripped off over large areas, whereas, in pemphigus vulgaris it is possible to strip only a limited area, which is really the exact area of the blister, the neighboring skin being abso-

38. Hallopeau, H., and Jousset: Ann. dermat. et syph. (Series 3) **7**:370, 1896.

39. Oliver, E. A.: Personal communication to the author.

40. Hollander, L., in discussion on Phillips, H. T.: Pemphigus (Chronic), Arch. Dermat. & Syph. **43**:1022 (June) 1941.

41. Mitchell, J. H., in discussion on Zeisler, E. P., and Bluefarb, S. M.: Melanoma, Arch. Dermat. & Syph. **49**:221 (March) 1944.

42. MacLeod, J. M. H.: Brit. J. Dermat. **27**:201, 1915.

lutely normal. Also, in pemphigus foliaceus, if the normal-appearing area between the lesions of the skin is rubbed, the stratum corneum comes off, while in pemphigus vulgaris, if the lesions are healed, this cannot be done. In the present day this sign is not only generally interpreted as a diagnostic measure for differentiating pemphigus foliaceus and pemphigus vulgaris, but also is used for the diagnosis of pemphigus vulgaris. It is not pathognomonic, however, for as Bechet stated, Nikolsky's sign may be found in diseases other than pemphigus.

6. Sensitivity to iodides and bromides: Felsher [43] has suggested that this reaction may be due to the changed electrolytic state of the collagen in these diseases, the iodide or bromide ions causing a powerful and still further reduction in the diminished adhesiveness of the dermis and epidermis. He stated that this reaction occurs in dermatitis herpetiformis and often in pemphigus. Azulary and Villela Pedras,[44] as the result of a series of tests, doubted the specificity of this test for dermatitis herpetiformis.

HISTOPATHOLOGY

There is considerable difference of opinion as to the value of the microscopic findings in the differential diagnosis of pemphigus and dermatitis herpetiformis. Raedeli, for example, stated that in the bullous stage, there is no difference.

Recently Dupont and Piérard [45] have found that, while the dermal changes in these two diseases are similar, histologic examination of the epidermis shows essential differences. Their work has been confirmed by Lapiere and others,[46] who found that in dermatitis herpetiformis the epidermis was completely separated from the underlying tissue and that the edges of the bullae were sharp, while in pemphigus Nikolsky's sign was always positive, the epidermis was fissured, and the border of the lesions ill-defined. Fassotte [47] also felt that the observations of Dupont and Pierard were significant, but Percival and Hannay [48] disagreed, feeling that neither the position of the bullae nor the presence or absence of epidermal tissue on its floor provided any features which enable us to distinguish one of the bullous diseases from another.

The following recent observations have been reported as of aid in diagnosis:

1. Mulvehill (1944) [49] studied the serum proteins in a number of dermatoses, and only in pemphigus found any significant changes for total proteins, serum-albumin and serum globulin. He found a consistent and significant fall in the serum-albumin fraction; and in the differential diagnosis of pemphigus and dermatitis herpetiformis and erythema bullosum, he feels that a serum-albumin level of 3.3 gm. or less should point strongly to pemphigus.

2. Cordero (1947) [50] based the diagnosis between pemphigus and dermatitis herpetiformis on smears of material obtained by scraping the floor of the lesions.

43. Felsher, Z.: J. Invest. Dermat. **8**:55, 1947.

44. Azulary, and Villela Pedras: Brazil dermat. e. sif. **24**:49, 1949.

45. Dupont, A., and Piérard, J.: Arch. belges dermat. et syph. **5**:275, 1949.

46. Lapiere, S., and others: Arch. belges dermat. et syph. **2**:51, 1946.

47. Fassotte: Arch. belges dermat. et syph. **4**:239, 1948.

48. Percival, G. H., and Hannay, P. W.: Brit. J. Dermat. **61**:42 and 77, 1949.

49. Mulvehill, W.: Serum Protein in Dermatoses, Arch. Dermat. & Syph. **49**:327 (May) 1944.

50. Cordero, A. A.: Rev. argent. dermatosif. **31**:578, 1947.

He stated that in pemphigus the bulla is formed by cleavage in the malpighian layer and that the dermal papillae are always covered by at least the basal layer, while in dermatitis herpetiformis the bulla is located between the detached epidermis and dermis. As stated in the discussion of the work of Dupont and Piérard mentioned above, there is not as yet general acceptance of any differences in the level of the bullae in these two diseases.

3. The similar observations of Tzanek [51] have received considerable recognition, although, as yet, no general acceptance. He stated that in pemphigus, upon scraping the floor of the lesions, one always finds recognizable malpighian cells readily, while in dermatitis herpetiformis, one sees mostly blood and nontissular cells and eosinophiles.

4. Canizares [52] has applied the McClure-Aldrich test by injecting isotonic sodium chloride solution intradermally in various diseases and measuring the disappearance time. Canizares feels that in the differential diagnosis of pemphigus and erythema bullosum a persistent rapid reading favors pemphigus, and one returning to normal as the patient gets better indicates erythema multiforme. In dermatitis herpetiformis the disappearance times are short during exacerbations and later return to normal.

In summary, then, one might say that in certain instances the clinical picture of a bullous dermatosis may be such that pemphigus and dermatitis herpetiformis, pemphigus and erythema bullosum, or all three diseases may have to be considered. Since none of the usually cited diagnostic criteria are rigid or dependable, only continued observation over a variable but often prolonged period may make a diagnosis possible. Since it is well known that patients with unquestionable pemphigus do recover, we must abandon the old statement that if the patient recovers, the original diagnosis was incorrect. Likewise, a fatal outcome does not establish the diagnosis, since patients with severe erythema bullosum sometimes die.

The question as to a possible relationship between dermatitis herpetiformis and pemphigus must remain unanswered at present. Michelson [53] believes that pemphigus and dermatitis herpetiformis are two different diseases, and that when one speaks of dermatitis herpetiformis changing into pemphigus one has merely made a mistake in the original diagnosis; but Stephan Epstein,[54] recalling a number of cases of typical dermatitis herpetiformis which ended fatally as pemphigus, is not sure that they are two different diseases. The older French school considered pemphigus foliaceus as an end stage of both pemphigus vulgaris and dermatitis herpetiformis, and more recently there has been some emphasis upon the unicist theory on the part of the French school. Nekam Jr. and Florian [32] believe that both pemphigus and dermatitis herpetiformis may be considered as manifestations of the same cause in persons of different constitution.

There is no space to discuss the special forms of pemphigus, but one may state that there is general accord in believing that pemphigus vegetans and pemphigus

51. Tzanek, A.: Ann. dermat. et syph. **8**:205, 1948.

52. Canizares, O.: J. Invest. Dermat. **13**:325, 1949.

53. Michelson, H. E., in discussion on Madden, J. F.: Case for Diagnosis (Pemphigus Vulgaris? Dermatitis Herpetiformis?), Arch. Dermat. & Syph. **50**:429 (Dec.) 1944.

54. Epstein, S., in discussion on Madden, J. F.: Case for Diagnosis (Pemphigus Vulgaris? Dermatitis Herpetiformis?), Arch. Dermat. & Syph. **50**:429 (Dec.) 1944.

foliaceus are but modified forms of pemphigus vulgaris, except for those cases of pemphigus foliaceus which begin as dermatitis herpetiformis. Pemphigus erythematosus is now, I believe, generally accepted as a definite type of pemphigus, and of pemphigus only. While often benign and of prolonged course, it may rapidly become, in some instances, pemphigus vulgaris or pemphigus foliaceus and follow the usual course of those diseases. We have recently had under observation a patient in whom a typical pemphigus erythematosus developed, succeeded by equally typical pemphigus chronicus. Various types of treatment were without effect until corticotropin was used. The patient then showed a remarkable improvement, but the disease, upon involuting, again assumed the form of and has persisted as pemphigus erythematosus.

In different countries, depending upon experience with a few cases of this uncommon but not-rare disorder, emphasis has been placed variously upon the bullous, foliaceous, or seborrheic aspects of the disease.

So much has been written recently about ocular pemphigus, that it is necessary only to refer to the articles of Klauder,[55] Lever,[56] Kanee[57] and others. They have pointed out that this is a more benign disorder than ordinary pemphigus, affecting chiefly women from the ages of 45 to 70. The lesions affect the mucous membranes particularly, chiefly those of the eyes, but at times the nose, throat, mouth, esophagus, vagina, and penis may be involved. When the skin presents lesions, as it does in about 50% of cases, these are usually limited to a few areas. We have under observation at present, however, a woman who has had typical ocular pemphigus for the past five to six years, for some time accompanied by only a few skin lesions; but for the past year the cutaneous involvement has been more extensive than that in most cases of ordinary pemphigus. While there has been reluctance to accept this disorder as a type of pemphigus, in late years there seems to be general agreement in feeling, as phrased by Lever, that the ocular type should be recognized as a special form of pemphigus in view of its benign course and its tendency to produce scars, as well as for its tendency, in some instances, to be limited to the conjunctivae.

With regard to *fogo salvagem*, the "wild fire" of Brazil, we have time only to say that, in spite of clinical resemblance to pemphigus foliaceus, the occurrence of the disease endemically, the frequency with which two or more members of a family are attacked, and the changes indicating endocrine disturbance, as evidenced by the occurrence of atrophy of the breasts and amenorrhea, would indicate that this is an independent disease.

THERAPY

Many agents have been used in the treatment of pemphigus, but the results with all of these have been inconsistent. Furthermore, in this field we find that measures which are favorably regarded in one section may not give good results in other places. An example of this is the David-and-Davis treatment consisting of

55. Klauder, J. V., and Cowan, A.: Ocular Pemphigus and Its Relation to Pemphigus of the Skin and Mucous Membranes, Am. J. Ophth. **25**:643, 1942.

56. Lever, W. L.: Pemphigus Conjunctivae with Scarring of the Skin, Arch. Dermat. & Syph. **49**:113 (Feb.) 1944.

57. Kanee, B.: Ocular Pemphigus with Scarring of the Skin and Mucous Membranes, Arch. Dermat. & Syph. **55**:37 (Jan.) 1947.

intravenous injection of ferric cacodylate and subcutaneous injection of coagulen® (a hemostatic preparation containing thromboplastic substances) on alternate days. A very high proportion of good results was obtained with this method in St. Louis, the city of its origin, and by Wende in Buffalo, but elsewhere the results were much less gratifying. In the same way, suramin (naphuride®) sodium, which at one time was widely used on the East Coast, did not seem as effective to those of us in this location. Likewise, the results with the use of large doses of vitamin D varied greatly in the experience of different observers.

It is unnecessary here to recite the various agents and methods of treatment which have been employed. Of course, the chief interest at present lies in the use of corticotropin, cortisone, and similar agents, but, as yet, it is too early to have a valid evaluation of their effects in pemphigus. In some centers the drugs have been used in a very intensive dosage, with some supposed cure obtained, while in most places they have been used in orthodox fashion. In our limited experience, the improvement secured has been dramatic, but complete clearing has not been obtained, and mild remissions have occurred even while the patients were on maintenance doses.

Treatments and medicaments which have been used include the following:

Stimulants: caffeine, strychnine, digitalis, epinephrine, and elixir of iron, quinine, and strychnine.

Supportive and "Specific" Remedies: arsenicals (potassium arsenite, ferric cacodylate, acetarsone, carbasone, phenarsone sulfoxylate, tryparsamide, etc.), quinine, methylene blue, suramin sodium, sulfonamides, adrenal cortical extract plus sodium chloride, synthetic oleovitamin D, ascorbic acid, dihydrotachysterol, convalescent serum, blood transfusions, autohemic therapy, antibiotics, proteins, x-ray treatment of kidney and spleen, diuretics, liver extract, bed rest, controlled fluid intake, high caloric diet, and acriflavine-moccasin-snake-venom.

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GENETIC ASPECTS OF MALIGNANT MELANOMA

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THE GENETIC aspects of cancer in general have been carefully sifted and scrutinized in the search for clues to the origin of malignant neoplasia, with some significant results. Heredity is recognized as the motivating factor in the evolution of retinoblastoma, but at the opposite end of the scale is cancer of the lip, which has been shown to occur without any inherited predisposition.[1] Between these two extremes is an intriguing array of data concerned with the role of heredity in the field of human cancer. These data are abundant in reference to some neoplasms, especially those occurring in "cancer families," but meager in regard to others, only the scantiest attention having been given to the hereditary features of malignant melanoma in humans.

In succeeding paragraphs will be described first the hereditary aspects of malignant melanoma in animals, since these shed light on the problem as it involves humans, followed by the presentation and discussion of data which show that a genetic influence must also be reckoned with in the occurrence of malignant melanoma in humans.

INFLUENCE OF HEREDITY ON OCCURRENCE OF MALIGNANT MELANOMA IN ANIMALS

The best experimental work on the genetic aspects of melanoma has been done by Gordon,[2] who has studied in detail the inheritance of melanoma in fishes. He has shown that melanomas develop in certain hybrid fishes in response to an imbalance between the genes for macromelanophores, five of which have been identified, and their growth regulators, specific macromelanophore-modifying genes, two of which are known. Gordon has also demonstrated that the amount of melanin

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1. Waaler, G. H. M., cited by Blank, F.: Genetic Aspects of the Cancer Problem, Arch. Surg. **49**:301 (Nov.) 1944.

2. (*a*) Gordon, M.: Effects of 5 Primary Genes on the Site of Melanomas in Fishes and the Influence of 2 Color Genes on Their Pigmentation, in Gordon, M., and others: The Biology of Melanomas, Special Publications, Vol. 4, New York Academy of Sciences, New York, 1948, p. 216; (*b*) The Origin of Modifying Genes That Influence the Normal and Atypical Growth of Pigment Cells in Fishes, in Proceedings of the Second Conference on Biology of Normal and Atypical Pigment Cell Growth; reprinted, Zoologica **35**, Pt. 1, 1950.

pigment elaborated in melanotic tumors in fishes is genetically controlled. Of special interest to clinical medicine, which has debated for many years the possible relationship of cutaneous to ocular melanomas in humans, is Gordon's observation that the genetic basis for ocular melanomas in fishes is completely independent of the hereditary factors for integumentary melanomas.[2a]

Burdette,[3] in experiments on the hereditary factors which control the occurrence of melanotic tumors in Drosophila, has been able in some instances not only to find the chromosome responsible for tumor susceptibility but also to determine the locations of the genes involved on a specific part of each chromosome.

Sheremetieva and Brunst [4] recently reported the discovery, among hundreds of Mexican axolotls (salamanders), of a male and female of the gray variety with infiltrating melanotic tumors on the sides of their bodies. These were mated, and among their offspring in three successive generations occurred a fairly large number of specimens with malignant melanomas. The neoplasms, through the axolotl's transparent epidermis, could be seen, even with the naked eye, invading surrounding normal tissues. These investigators remarked on the different growth rates of the tumors in the various generations. The first two specimens had slowly growing melanomas, while those in the offspring grew much faster and reached a much greater size.

The Cloudman mouse melanoma, which metastasizes, can be successfully transplanted into other members of its own genetic strain only (dba mice), as compared with the Harding-Passey mouse melanoma, which is not malignant, and can be transplanted into several strains of mice. Genetic factors evidently control the peculiar susceptibility of dba mice to the Cloudman melanoma.

In 1946 Ball [5] described the occurrence of a malignant melanoma of the tail in a female pine snake, with metastases to the head and abdominal wall. All lesions were removed by electrocautery, and two months later the snake produced six normal offspring. Later the same female was mated with a male pine snake which had a melanoma of the labial fold. Three offspring of this mating had abnormal eyes. Ball suggested that the blindness of the young indicated a possible genetic effect of disturbed pigment metabolism in the parents. In this careful study of reptilian melanomas in general, Ball found no support for Laidlaw and Murray's suggestion [6] that the human pigmented mole is a phylogenetic tumor representing an abortive tactile spot related to the well-developed structures which are normal in reptiles.

Caylor and Schlotthauer [7] observed three cases of malignant melanoma of the skin in swine of the same breed and same herd, and in each instance the tumor occurred in the skin of the right flank. The three swine had a common sire, and

3. Burdette, W. J.: Melanotic Tumors in Drosophila, in Proceedings of the Second Conference on Biology of Normal and Atypical Pigment Cell Growth, reprinted from Zoologica **35**, Pt. 1, 1950.

4. Sheremetieva, E., and Brunst, V. V.: Spontaneous Tumors in Axolotls, Proc. Conf. Med. Biol. **1**:143, 1936 (in Russian with English summary); cited by Gordon.[2]

5. Ball, H. A.: Melanosarcoma and Rhabdomyoma in 2 Pine Snakes, Cancer Res. **6**:134 (March) 1946.

6. Laidlaw, G. F., and Murray, M. R.: Melanoma Studies III. A Theory of Pigmented Moles: Their Relation to the Evolution of Hair Follicles, Am. J. Path. **9**:827 (Nov.) 1933.

7. Caylor, H. D., and Schlotthauer, C. F.: Melano-Epithelioma of Swine: Transplantation and Cultural Experiments, Arch. Path. & Lab. Med. **2**:343 (Sept.) 1926.

two of them the same mother. The mother of the third was a sister of the sow which had farrowed the first two. Each of the animals, two males and a female, was about 6 weeks old when the tumors were first noted. The testicles of the males were removed, and these animals grew at the same rate as the rest of the herd. When they were killed, some time later, metastases were present, but these did not extend beyond adjacent lymph nodes. The female swine, on the contrary, lost weight and became debilitated, and, upon autopsy, was found to have widespread metastases. This suggested to the authors the probable influence of castration on the growth and spread of the tumor. It is apparent that hereditary factors influenced the occurrence of these three melanomas.

The greatest number of melanomas among animals occur in horses.[8] Anatomically the sites of predilection are the skin of the ventral surface of the tail, the anal region, the vulva, the scrotum, and the region of the perineum. The tumors vary as to degree of cancerousness, but do metastasize. As early as 1781 Brugnone [9] described anal melanomas in gray horses and recognized the inheritability of the tumors, and Gohier [10] noted in 1813 that malignant melanomas were especially common in old gray horses. Virchow [11] recorded a case in which a young white stallion with a melanoma of the anal region transmitted the neoplasm to all its white descendants, whereas those of a dark color escaped. In recent years it has been shown that the tendency for development of melanomas in gray horses increases with age and the associated gradual loss of pigment of the hair which causes the horses to become white, but the exact genetic mechanism is not clear. Van Dorssen's data [12] indicate that all gray horses are afflicted with malignant melanoma if they live to an old age. The tumors do occur at times in brown, red, and black horses, but only very infrequently. Breed and sex are apparently of no significance in the etiology of malignant melanomas in horses. The conclusion cannot be avoided that the evolution of malignant melanomas in horses is controlled by the same, or intimately related, genetic factors which determine the color of the animals. In view of the frequent origin of malignant melanomas of the skin of humans from pigmented nevi, and the common occurrence of melanomas in old gray and white horses, it is worth pointing out that Jaegers [13] was unable to find a single pigmented nevus of the skin in the postmortem examination of 63 old gray and white horses.

Malignant melanomas are uncommon in cattle. Imminger [14] observed that they are more frequent in white than in dark cattle, a situation not unlike that which exists in humans, malignant melanomas being far commoner in light- than in

8. Feldman, W. H.: Neoplasms of Domesticated Animals, Philadelphia, W. B. Saunders Company, 1932.

9. Brugnone, cited by Pack, G. T., and Livingston, E. M.: The Treatment of Pigmented Nevi and Melanomas, in Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940.

10. Gohier, cited by Feldman.[8]

11. Virchow, cited by Williams, W. R.: The Natural History of Cancer, W. Heinman, London, 1908.

12. Van Dorssen, cited by Feldman.[8]

13. Jaegers, cited by Feldman.[8]

14. Imminger, cited by Feldman.[8]

dark-skinned persons. Malignant melanomas of both the skin [15] and the eye [16] also occur in dogs, but they are very rare, and there is no convincing evidence which points to a hereditary influence. Malignant melanomas have been observed on rare occasion in other animals, including mules, rabbits, cats, and chickens, but there has been nothing to suggest that heredity played a role in the occurrence of the tumors in these animals.

SOME GENETIC ASPECTS OF MALIGNANT MELANOMA IN HUMANS

Only a few examples of malignant melanoma of the eye in humans have been reported in which genetic factors were significant. The pertinent features of these cases are presented here briefly.

Davenport [17] described a remarkable family with malignant melanoma of the eye in which it cannot be doubted that genetic factors exerted the most profound influence. The first case was in a woman aged 38, whose left eye was removed for malignant melanoma in 1871 and who died seven months later with metastases. Two of her daughters also had malignant melanoma of the eye. One had the left globe enucleated in 1899 at the age of 19 and died five years later of metastases. An elder daughter had her left eye removed in 1904 at the age of 38 and died of metastases in 1905. In the only two daughters of the last patient malignant melanoma of the eye also developed. One had her right eye enucleated in 1918 at the age of 29 and died of metastases four years later. The other had the right globe removed in 1914 at the age of 19. Nine years later metastases first appeared in the skin of the right arm. She was still alive in 1925, with metastases.

Delayed metastatic growth, as occurred in the last case, is not unusual with malignant melanoma, casting doubt on many so-called "five year cures."[18] Wilbur and Hartman [18] emphasized that when one is confronted with a patient with a glass eye and a large abdomen or liver the suspicion should immediately be aroused that a malignant melanoma has metastasized, regardless of the number of years since enucleation of the globe.

In 1892 Silcock [19] presented two specimens of "melanotic sarcoma of the eyeball" before the Pathological Society of London. The first was from the left eye of a young woman aged 20. The second specimen was from the left eye of the mother of the first patient, and the growth was similar in position and structure to the first. The neoplasm in the case of the mother was discovered about a year before the birth of the first patient. These specimens were presented because they raised a question of whether there was any hereditary vulnerability of the eye tissues to melanotic sarcoma in this family. Silcock's report has been referred to by several authors, two of whom [20] have noted that the maternal grandfather of the first

15. Mulligan, R. M.: Neoplastic Diseases of Dogs: I. Neoplasms of Melanin-Forming Cells, Am. J. Path. **25**:339 (March) 1949.

16. Bloom, F.: Melanocarcinoma of the Iris in a Dog, J. Am. Vet. M. A. **100**:439 (May) 1942. McCelland, R. B.: Melanosis and Melanomas in Dogs, ibid. **98**:504 (June) 1941.

17. Davenport, R. E.: A Family History of Choroidal Sarcoma, Brit. J. Ophth. **11**:443 (Sept.) 1927.

18. Wilbur, D. L., and Hartman, H. R.: Malignant Melanoma with Delayed Metastatic Growths, Ann. Int. Med. **5**:201 (Aug.) 1931.

19. Silcock: Report of Pathological Society of London, Brit. M. J. **1**:1079 (May 21) 1892.

20. (*a*) Pfingst, A. O., and Graves, S.: Melanosarcoma of the Choroid Occurring in Brothers, Arch. Ophth. **50**:431 (Sept.) 1921. (*b*) Wintersteiner, cited by Pfingst.[20a]

patient died of a melanoma of the choroid. Silcock's report emphasizes that the grandfather had lost an eye but that there was no evidence to indicate that it was due to neoplasm. Nevertheless, the occurrence of such a relatively rare tumor as malignant melanoma in the same eye of even two members of the same family, at about the same age, is strong presumptive evidence of a hereditary influence.

Pfingst [20a] reported the occurrence of a "melano sarcoma" of the left eye in a 44-year-old farmer and also in the left eye of this patient's 47-year-old brother. Both neoplasms were discovered at about the same time. Another brother, aged 37, and a sister, aged 50, were normal. Pfingst was evidently uncertain about the influence of heredity on the occurrence of these two malignant melanomas in the eye but concluded that the event could probably best be interpreted as a rare coincidence. As with Silcock's cases, it seems clear that the occurrence of malignant melanoma of the same eye in brothers, at about the same time in life, is probably more than a coincidence and can best be explained on genetic grounds.

In 1926, Parker and Stokes,[21] under the title "Intraocular Sarcoma in Children," described 10 children with malignant neoplasms of the eye. In two instances the patients were sisters, each having both eyes affected. The latter two cases are cited [22] in a tabulation of cases which illustrate the effect of heredity on the occurrence of malignant melanomas of the eye. A review of Parker and Stokes's communication indicates, however, that the neoplasms in the two cases in question, as well as those in the other eight cases described, were probably examples of retinoblastoma, and not malignant melanoma. There is little doubt that many other ocular neoplasms catalogued in the past as examples of malignant melanoma, especially those occurring in children, would have been classified as cases of retinoblastoma in the light of present knowledge.

Lastly, Waardenburg [23] described in 1940 the occurrence of a "melanosarcoma" of the right eye in an uncle and a niece. The diagnosis in the second case was made after an interval of 15 years. The evidence favoring a genetic influence in these two cases is not convincing.

With the exception of the three cases to be described below, there are no recorded examples of malignant melanoma of the skin in humans, the occurrence of which has been manifestly influenced by hereditary factors.

REPORT OF THREE CASES OF MALIGNANT MELANOMA OF THE SKIN IN ONE FAMILY

CASE 1.—L. M., aged 60, a white salesman, was admitted to the University of Michigan Hospital on Jan. 2, 1950. He had had a dark-brown papule, about 1.5 cm. in diameter, on his left forearm for the past year. Three weeks before admission the lesion increased rapidly in size and became intensely black. It was removed by wide surgical excision. Upon microscopic examination the lesion presented the features of a malignant melanoma (Fig. 1).

21. Parker, W. R., and Stokes, W. H.: Intra-Ocular Sarcoma in Children, J. A. M. A. **87**:1891 (Dec. 4) 1926.

22. Macklin, M. T.: Genetic Aspects of Pigment Cell Growth in Man, in Gordon, M., and others: The Biology of Melanomas, Special Publications Vol. 4, New York, New York Academy of Sciences, 1948, p. 144.

23. Waardenburg, P. J.: Melanosarcoma of the Eye in More Than One Member of a Family, Nederl. tijdschr. geneesk. **84**:4718 (Nov. 30) 1940; abstracted in Am. J. Dis. Child. **63**:193 (Jan.) 1942.

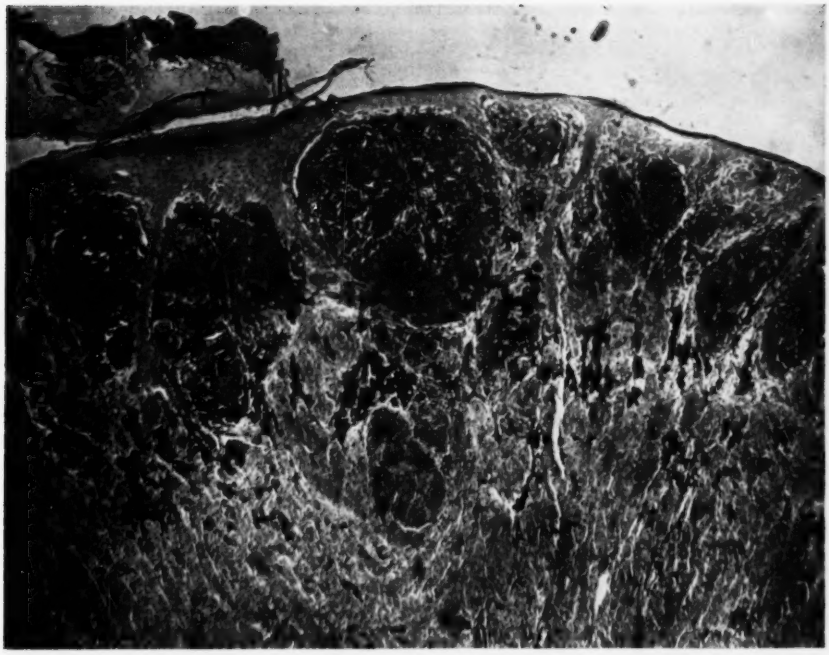

Fig. 1 (Case 1).—Low-power photomicrograph of the primary lesion from the arm. The neoplastic cells were of the epithelioid type.

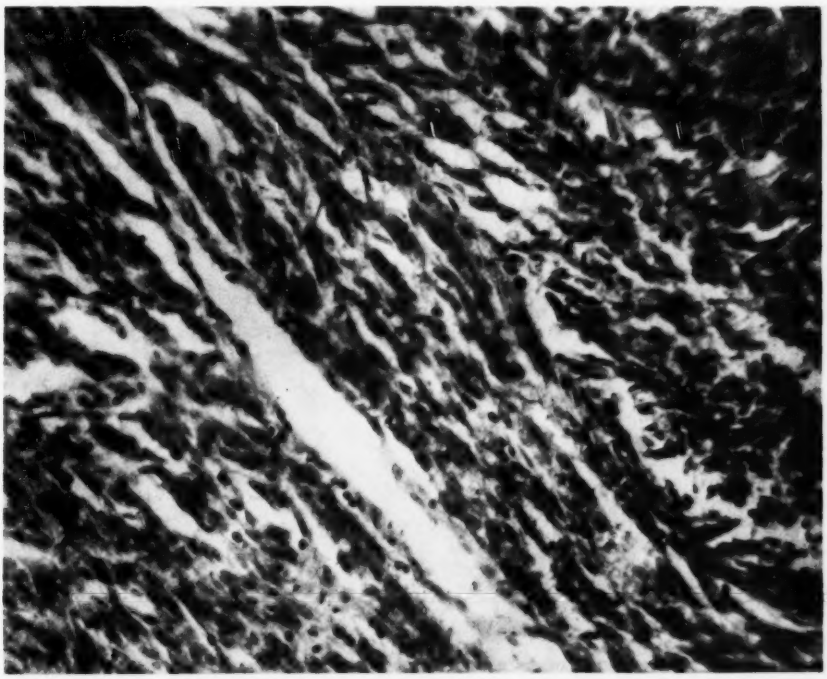

Fig. 2 (Case 1).—High-power photomicrograph showing metastatic malignant melanoma in the axillary node. Neoplastic cells were spindle-shaped; a metastatic node removed from the right inguinal region of the same patient at a later date showed neoplastic cells of the epithelioid type, resembling those of the primary lesion

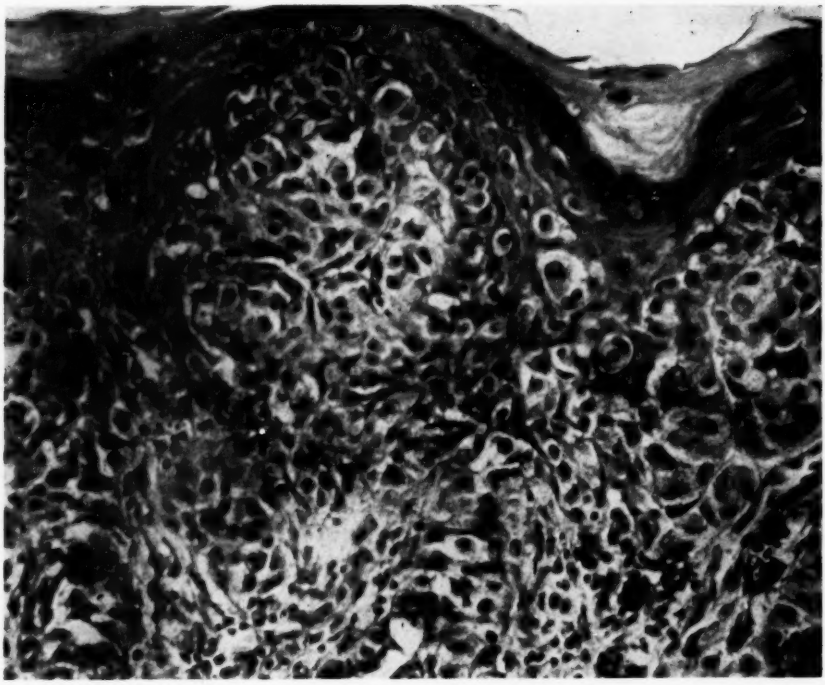

Fig. 3 (Case 2).—High-power view of a portion of the primary lesion.

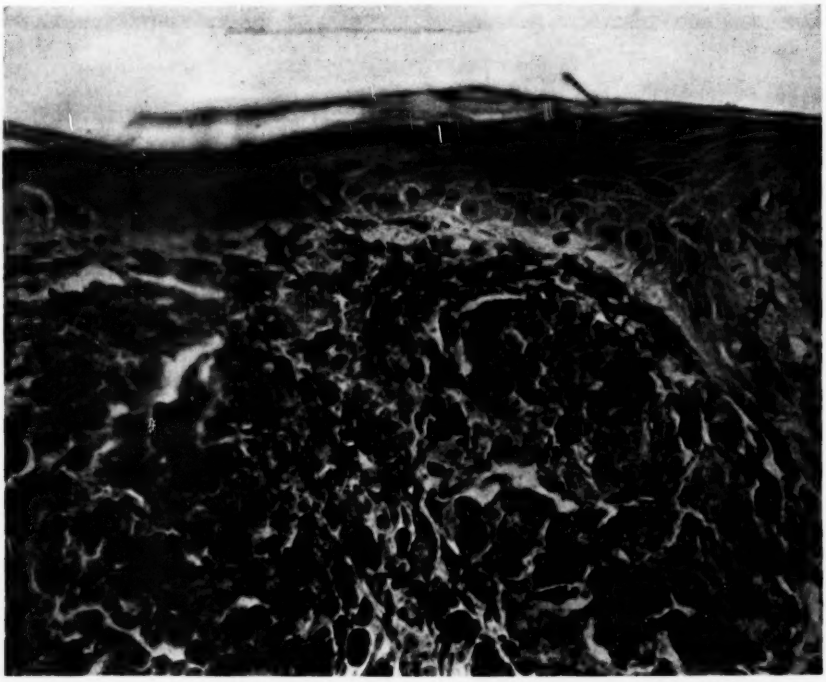

Fig. 4 (Case 3).—High-power view of a portion of the primary lesion. Many large clods of pigment were present in the neoplasm.

Physical examination at the time of admission showed the patient to be in apparent good health. He had light-red hair, blue eyes, and a "sandy" complexion. There were three seborrheic keratoses on the forehead and two pigmented nevi on the trunk. No lymph nodes were palpable. Results of laboratory studies were normal.

On Jan. 3, 1950, a left epitrochlear and left axillary lymph-node dissection was performed. In one of the 10 sections of lymph nodes from the axilla was found metastatic spindle-celled malignant neoplasm (Fig. 2). The patient's progress appeared to be satisfactory, but on Sept. 1, 1950, he was operated upon again because of the sudden appearance of a hard nodule about 2 cm. in diameter in the right inguinal region. This, too, was found to be a metastasis. Upon microscopic examination of this node there were seen to be scattered collections of melanin, and the neoplastic cells were of the epithelioid type, resembling those of the primary lesion, as contrasted with those of the axillary metastasis which, as previously noted, were spindle-shaped.

The patient was alive and in apparent good health, with no further demonstrable metastases, in April, 1951.

CASE 2.—H. M., aged 24, a white clerk, was the son of L. M. (Case 1). He had had a soft, brown, papular nevus on the right side of the abdomen since the age of 3 or 4 years. In March, 1948, the lesion had attained a size of 1 by 1.5 cm. and was black and soft. It was removed by wide surgical excision. Findings on microscopic examination were compatible with a diagnosis of malignant melanoma arising in a pigmented nevus (Fig. 3).

In June, 1949, the patient noticed a swelling in the right inguinal region. He was admitted to the University of Michigan Hospital on Nov. 30, 1949. Physical examination revealed a hard, freely movable node, about 3 cm. in diameter, in the right inguinal region. There were multiple soft brown nevi on the trunk and extremities. The patient had light hair, blue eyes, and a "sandy" complexion like that of his father. Results of all laboratory studies were normal.

A radical operation was done in the right inguinal region and pelvis on Dec. 2, 1949. Microscopic examination showed heavily pigmented metastatic melanoma replacing the large lymph node previously described, but 14 other nodes were free of neoplasm. The patient recovered promptly from the operation, but his general health soon began to deteriorate; his liver enlarged tremendously, and he died of metastatic melanoma on Jan. 22, 1950.

CASE 3.—D. C., aged 31, a white housewife, was the daughter of L. M. (Case 1) and the sister of H. M. (Case 2). In December, 1949, during the last few weeks of her second pregnancy, she noticed a sudden and rapid increase in size and depth of color of one of the nevi which had been present as long as she could remember on the lateral aspect of the right leg.

Physical examination showed a firm black papule, 1 by 1.5 cm. in size, on the lower right leg. There were numerous brown nevi scattered on the trunk and extremities, and the patient stated that the lesion on the leg had formerly been of the same type. There were no palpable lymph nodes, and the results of all laboratory studies were normal. She had light hair, blue eyes, and a fair complexion, just as did her father and brother.

On Jan. 20, 1950, the lesion was removed by wide surgical excision. Findings upon microscopic examination were commensurate with a diagnosis of malignant melanoma arising in a junction nevus (Fig. 4). The patient was alive and well in January, 1951, with no demonstrable evidence of metastases.

COMMENT

Experimental studies on the genetic aspects of melanomas in certain fishes, Drosophila, the Mexican axolotl, and mice, as well as observations on the spontaneous occurrence of melanomas in horses, swine, and snakes, have forcibly demonstrated the influence of heredity on the occurrence of malignant melanoma in these animals. A few examples of malignant melanoma of the eye in humans have been reported in which genetic factors were significant, but with the exception of the three cases described in this paper there are no recorded examples of

malignant melanoma of the skin in humans, the occurrence of which has been manifestly influenced by hereditary factors.

The sporadic occurrence of cancer in more than one member of a family is scarcely remarkable when it is recognized that one in every 8 or 10 persons who lives past the age of 40 dies of cancer.[24] Considering the variety of neoplasms which exist and the many structures and organs which may be involved, however, it is indeed remarkable that three members of the same family should have the same type of relatively rare cancer (malignant melanoma) involving the same organ (skin) (Fig. 5). On statistical grounds it can be calculated that the probability of at least one family of five members[25]—there were five members in the family described—having three cases of malignant melanoma of the skin is 4.4 in a billion, a figure which statisticians regard as far outside the realm of chance.[26] Heredity, not the other intrinsic or extrinsic factors in the origin of cancer, and not chance, was evidently the noxious agent in the three cases recorded above. As an anticlimax to this statement, however, it must be pointed out that any simple Mendelian interpretation of the influence exerted by heredity in these three

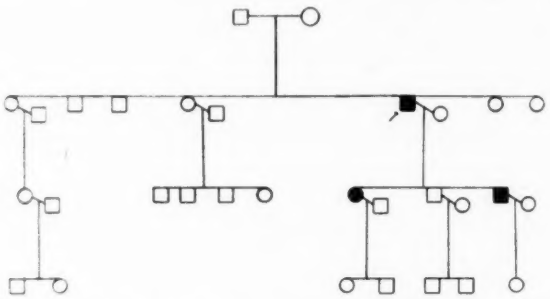

Fig. 5.—Pedigree of the family described; shaded symbols indicate melanoblastoma. The father (Case 1) is indicated by the arrow and black square, the son (Case 2) by the lower black square, and the daughter (Case 3) by the black circle.

cases, which reduces the problem to terms of definite genes, is impossible in the light of present knowledge, just as with human cancer in general.[27]

SUMMARY

1. Experimental studies and clinical observations show a definite relationship between hereditary factors and the occurrence of malignant melanomas in animals.

2. Data presented on three cases of malignant melanoma of the skin in the same family show evidence that similar genetic factors must also be reckoned with in humans.

University of Virginia.

24. Macklin, M. T.: The Hereditary Factor in Human Neoplasms, Quart. Rev. Biol. **7**:255 (Sept.) 1932.

25. Considering 200,000 or more such families.

26. These calculations were performed by the Laboratory of Statistical Research, University of Michigan.

27. Waaler, G. H. M.: Über die Erblichkeit des Krebses, Naturv. Klasse, 1931, no. 2, p. 78; abstracted in Cancer Rev. **70**:464, 1932.

ABSTRACT OF DISCUSSION

DR. THOMAS B. FITZPATRICK, Rochester, Minn.: Dr. Cawley has presented an excellent review of genetic factors in animal and human ocular melanomas and has recorded the first cases of cutaneous melanoma occurring in a single family. I am sure that this report will stimulate physicians to search for other instances of familial melanomas, and no doubt many more such case reports will be forthcoming. About two weeks before this meeting, Dr. Montgomery and I saw a 2-year-old girl at the Mayo Clinic with a primary malignant melanoma of the skin, and the father, being a physician, called our attention to the fact that his grandfather had had a primary melanoma on the face and ultimately succumbed to complications associated with metastatic melanoma. Dr. Montgomery and I examined the child's two siblings and the father, and all three presented pigmented lesions on the palms and soles, which were shown by biopsy to be lentigines.

I wish to emphasize the remarkable incidence of melanomas in horses. The veterinary pathologists state that if a gray horse lives long enough, it will ultimately die of a malignant melanoma. Horse melanoma has a histologic picture which is identical with human tumor; metastasis is widespread, often involving the heart muscle as in human metastatic melanoma. Furthermore, horse melanoma contains an active tyrosinase system which is similar to the human malignant melanoma (Fitzpatrick, T. B.; Lerner, A. B.; Calkins, E., and Summerson, W. H., *Proc. Soc. Exper. Biol. & Med.* **75**:394, 1950). Horse melanoma, therefore, offers a unique opportunity to students of melanomas for a prolonged and careful study of the biology of malignant melanoma as it occurs spontaneously in mammals. No doubt the technical difficulties associated with the large size of the animal, such as care and feeding, and difficulty of necropsy, have prevented a thorough study of this remarkable animal tumor.

DR. UDO J. WILE, Ann Arbor, Mich.: The three patients about whom Dr. Cawley has told you have been under my observation now for about one and one-half or two years. It is interesting that the son died prior to the discovery of the pigmented moles which were thought to be potentially malignant in the father and found to be so after the son's death. Now then, in the very recent few weeks the father has presented himself again. He was found to have a large mass in the abdomen which was thought to be a metastasis. It was removed and found to be a large mass of fat in which there was a single metastatic lesion. Therefore, we believe that he too will ultimately die of this condition.

DR. JOSEPH V. KLAUDER, Philadelphia: There are two phases of this interesting and well-presented paper that I would like to discuss. One is malignant melanoma of the eye which arises most frequently in the choroid and at times from pigmentary deposits in the conjunctiva, which I imagine are in the nature of nevi. I think I see as many malignant melanomas of the eye, among patients in Wills Hospital, as I do of the skin. I would guess that the incidence of malignant melanomas stands high among all tumors of the eye. The other phase of my discussion concerns comparative dermatology in which I have been interested, especially in relation to erysipeloid (Erysipelothrix rhusiopathiæ infection) of man and swine. I am glad to note that on the program of this meeting there are two papers regarding comparative dermatology.

If the field of dermatology is to broaden, it could well include at least certain phases of cutaneous diseases of animals. Yesterday Dr. Gans made reference to Hebra's concept that no disease is complete unless its histologic picture is visualized. I may state in a similar way that no study of a disease is complete unless it is visualized in its manifestations in all animals. For example, consideration of eosinophile granuloma is not complete without reference to what is called syphiloid of cats, which comotes an eosinophile granuloma.

I can refer pertinently to Heller's chapter on skin diseases of animals in Jadassohn's handbook. It is interesting to note that in the Veterinarian School of the University of Pennsylvania there is now a staff member, a veterinarian, whose particular interest is cutaneous diseases of animals.

DR. A. R. WOODBURNE, Denver: I also am interested from the comparative dermatologic standpoint. I have raised Dalmatian dogs for some 20 years and want to add a few statistics on melanotic tumors in those animals. Some 10 or 15 years ago I had a bitch in which a melanotic tumor developed in the flank. The Dalmatian, as you know, is a black and white dog.

We removed the tumor, and histologically it was an extremely malignant melanoblastoma. However, simple excision was all that was necessary, despite the histologic appearance of extreme cancer. Metastatic lesions did not develop.

Later she had pups, and melanotic lesions developed in two of the pups when they were quite young. Histologically these lesions appeared quite malignant but did not metastasize, at least not while I knew about them. I wondered if that might not be the case in horses. They may appear malignant histologically, but I would like to know the outcome. Do they metastasize as they do in humans? I am sure they do not in dogs.

DR. L. H. WINER, Beverly Hills, Calif.: The histologic diagnosis of malignant melanoma is at times difficult. In addition, the degree of cancerousness is not indicated by the type of cells, as was demonstrated by the spindle-type cells in Dr. Cawley's case. It is assumed by some that the spindle-cell type is more malignant than the epithelial-cell type. But this is not the case. Cases of melanoma in the same family have been brought to my attention by Dr. Richard Steves, who reported that two sisters in Wisconsin both died of malignant melanoma, and more recently by Dr. J. Scholtz of Pasadena, Calif., who informed me of twins both having malignant melanoma.

DR. FRED D. WEIDMAN, Philadelphia: I am surprised that there are so many comparative dermatologists in this audience. For about 10 years I spent nearly 50% of my time performing necropsies upon wild animals in the Philadelphia Zoological Garden. During that time I did not see any malignant melanomas in them (Schlumberger, H. G., and Lucké, B.: Tumors of Fishes, Amphibians, and Reptiles, *Cancer Res.* **8**:657 [Dec.] 1948), although I saw a few in horses, and malignant melanomas are reported in snakes.

It is curious that there should be such a gap in the incidence of malignant melanomas between the fish, which is certainly a wild animal, and the incidence in horses and in man. Incidentally, I am unaware that melanomas metastasize in horses. Dr. Fitzpatrick commented on the difficulty in performing necropsies on horses. At the Zoological Garden we do not stop at an elephant. The animal is dragged to the stable yard, and a derrick is erected over it. The horse is "small fry."

DR. EDWARD P. CAWLEY, Charlottesville, Va.: I thank the discussers for their instructive comments. Mulligan (*Am. J. Path.* **25**:339 [March] 1949) recently described 36 melanomas, 19 of them "cancerous," which occurred in dogs. Six of these showed metastases at autopsy. A discussion of malignant melanoma in dogs was not included in this presentation because evidence of a genetic influence is lacking. The melanomas which occur in horses vary considerably as to degree of cancerousness, but most metastasize sooner or later.

AMYLOIDOSIS CUTIS: A MACULAR VARIANT

LAURENCE L. PALITZ, M.D., Ph.D.
AND
SAMUEL PECK, M.D.
NEW YORK

AMYLOID deposits are found in the skin in many diverse and unrelated conditions. The skin is rarely involved in the secondary systemic amyloidosis following chronic wasting diseases, but more often accompanies primary systemic amyloidosis with macroglossia. These comparatively rare conditions apparently have no connection with each other nor with the common localized amyloidosis cutis with which we are concerned in this report.

First described as amyloidosis cutis nodularis et disseminata by Gutmann [1] in 1928 and as lichen amyloidosis by Freudenthal [2] in 1930, this disease has been the subject of many reports in this country and abroad. Several varieties have been reported. In all these cases the lichenoid character of the primary lesion has been emphasized. This primary lesion has been described by Andrews [3] as a "small brownish, and slightly scaly papule which seems to be translucent and simulates a vesicle, but the fully developed papules are 2 mms. or more in diameter." From this basic papule the common forms of amyloidosis cutis are believed to evolve. These forms fall into three large groups [4]:

1. There is a papular form in which the papules do not coalesce but retain their individual state. The papules occur in groups usually on the lower legs but also on the forearms, thighs, and lower back. They are most commonly pinhead size, but may be larger, are brownish in color, and have a shiny flat-topped appearance. In this stage they can be distinguished from lichen planus by color and by absence of geometric outline and central delling. These papules can progress further while still retaining their singularity by becoming more elevated, by developing conical

From the Department of Dermatology, Mount Sinai Hospital.

Read before the New York State Medical Society, Buffalo, May 4, 1951.

1. Gutmann, C.: Amyloid of Skin: 2 Cases, Nederl. tijdschr. geneesk. **2**:4480 (Sept. 8) 1928.

2. Freudenthal, W.: Amyloid in der Haut, Arch. Dermat. u. Syph. **162**:40, 1930.

3. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 639.

4. (*a*) Winer, L. H.: Local Amyloidosis of the Skin, Arch. Dermat. & Syph. **23**:866 (May) 1931. (*b*) Nomland, R.: Localized (Lichen) Amyloidosis of the Skin: Report of 2 Cases, ibid. **33**:85 (Jan.) 1936. (*c*) Philpott, O. S., and Freshman, A. W.: Amyloidosis Cutis; Lichenoides, ibid. **33**:970 (June) 1936. (*d*) Abramowitz, E. W., and Isaak, L.: Lichenoid Amyloidosis, ibid. **40**:13 (July) 1939. (*e*) Dowling, G. B., and Freudenthal, W.: Lichen Amyloidosis, Proc. Roy. Soc. Med. **32**:1029 (July) 1939. (*f*) Dostrofsky, A., and Sagher, F.: Localized Amyloidosis of Skin: Report of Cases, Arch. Dermat. & Syph. **44**:891 (Nov.) 1941.

and verrucous surfaces, and by peripheral extension finally forming potato-grater-like plaques on the legs and thighs.

2. Another common form of amyloidosis cutis resembles hypertrophic lichen planus. In this type the basic papules coalesce to form small aggregates usually scattered over the lower legs. These aggregates are pea- to dime-sized, sharply circumscribed, elevated patches which may become lichenified, are often brownish to

Fig. 1 (Case 1).—Ill-defined plaques composed of pigmented macules with the shiny overlying skin characteristic of macular amyloidosis cutis.

purplish, and may simulate hypertrophic lichen planus to the extent that only histological section can differentiate the two diseases.

3. The third common type is an extension of the form described above in which the aggregates of papules and the lichenification are such as to suggest strongly the diagnosis of lichen chronicus simplex (Vidal). Here again biopsy or the intradermal Congo red test of Bennhold and Nomland may be necessary for differentiation.

The following two cases of histologically proved amyloidosis cutis differ clinically from the previously reported cases.

REPORT OF CASES

CASE 1.—A. F., a 47-year-old Puerto Rican woman, was first seen in the Skin Clinic of Mount Sinai Hospital complaining of itching of the legs of many years' duration. The serologic reaction for syphilis was negative. A complete blood count and the results of urinalysis were normal. The skin was generally dry. On the lower legs were ill-defined plaques of closely aggregated brownish macules, with an interlacing network of normal skin. Overlying the plaques, the skin was tight and shiny and appeared to be slightly translucent. The plaques were 10 to 50 cm. in length with indistinct outlines which shaded off into normal surrounding skin.

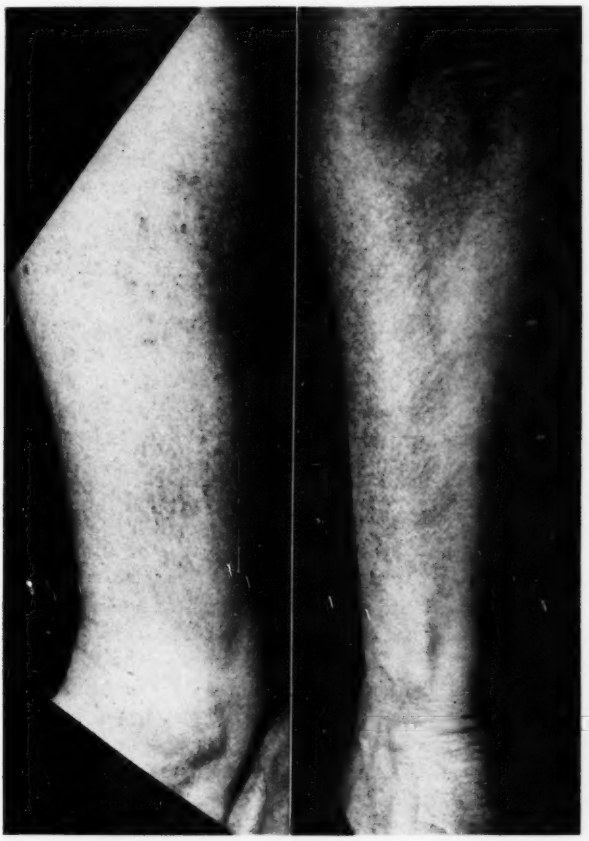

Fig 2 (Case 2).—Plaques of macular amyloidosis; left, lower leg; right, forearm.

The plaques had been extending in size in recent years. A biopsy revealed typical amyloidosis cutis (Fig. 1).

CASE 2.—A. C., a 37-year-old Puerto Rican woman, was inadequately treated for syphilis in 1942. Since 1947 she has had a full course of bismuth, oxophenarsine (mepharsen®), and penicillin at Mount Sinai Hospital. The serologic reaction for syphilis is still weakly positive. For the past six years the patient has been complaining of itching on the arms and legs. She presented many ill-defined shiny plaques of pigmentation on the lower legs and the extensors of both forearms. The plaques were composed of brownish small-pea-sized macules with interlacing normal skin. Laboratory studies showed the blood count and urine to be normal. A biopsy revealed typical amyloidosis cutis (Fig. 2).

COMMENT

The presenting complaint in both patients was intense itching. On physical examination their skins were noted to be generally dry. The lesions on the legs, and in one patient the arms, gave the clinical impression of ichthyosis. There was no papulation. In both cases the clinical picture was identical, although in one (Case 2) the condition was more widespread and involved the extensor forearms as well as the lower legs. It may be of significance that both patients were of Puerto Rican extraction and middle-aged women. There was no history of other members of their respective families being similarly afflicted.

It is our impression that the possibility of amyloidosis cutis in many such cases is overlooked because of the lack of papulation. And yet on close observation these cases present a definite clinical picture. Ill-defined areas of closely aggregated pigmented pinhead- to pea-sized macules, with interlacing normal skin and a shiny overlying surface should suggest the diagnosis of macular amyloidosis cutis. This diagnosis can be easily confirmed by biopsy or by the intradermal Congo red test of Bennhold and Nomland.

Two cases have been reported previously in the literature which mention the presence of macular forms of localized amyloidosis cutis without systemic involvement. The over-all picture in both cases, however, in no way resembles that in the two reported above. Koenigstein, in the Jadassohn Handbuch,[5] described a case of of Freudenthal's with reticular areas of bluish, livid, shiny discolorations composed of "hardly perceptible nodules with slight central depressions" on the dorsa of the feet. Histologically these lesions showed moderate hyperkeratosis and a thickened epidermis. Under the epidermis was a lymphocytic infiltrate, and under the infiltrate, an appreciable amount of amyloid. The elastic fibers were not changed. Gutmann's case, also referred to in the Handbuch,[5] was of one and one-half years' duration. There were lesions on the wrists, forearms, lower legs, and feet, with two distinct types of lesions side by side. Diffuse, round, reddish areas of livid discoloration were composed of pinhead and pinpoint, brownish-red, hardly perceptible macules. Above these areas the skin was slightly wrinkled. These macular areas showed a tendency to confluence. On the feet some discolored plaques were elevated above the surrounding areas. There were also some dense bullae present on the feet. Histologically, the epidermis was normal and the papillae flattened. The amyloid distribution was diffuse, not close to the papillary bodies but occupying, more or less, most of the upper cutis. There was a lymphocytic infiltrate. It is evident that in both of these cases the histological picture was not characteristic of amyloidosis cutis in that the amyloid deposits were not in masses directly below the epidermis and in both cases a lymphocytic infiltrate was a prominent feature.

HISTOLOGICAL STUDIES

The characteristic microscopic picture of localized amyloidosis cutis consists of masses of amyloid in the papillae directly below the epidermal layer and a moderate hyperkeratosis, acanthosis, and later atrophy of the epidermis. According to Nomland,[4b] the earliest lesions occur around the capillaries of the papillae. It is his belief that the amyloid substance is not deposited into the tissue spaces but infil-

5. Koenigstein, H., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, Vol. 4, Pt. 3, p. 334.

6. Footnote deleted.

trates into cells about the capillaries. As evidence for this supposition he cites the pathological picture of a pinpoint-sized lesion which showed amyloid present about the capillary of a single papilla. Here the amyloid appeared to be laid down in "preformed corpuscular bodies, the size and shape of which suggested cells with completely degenerated nuclei." This theory is further substantiated by Ebert [7] who, in the discussion of Nomland's excellent paper, cites the work of Smetanka in

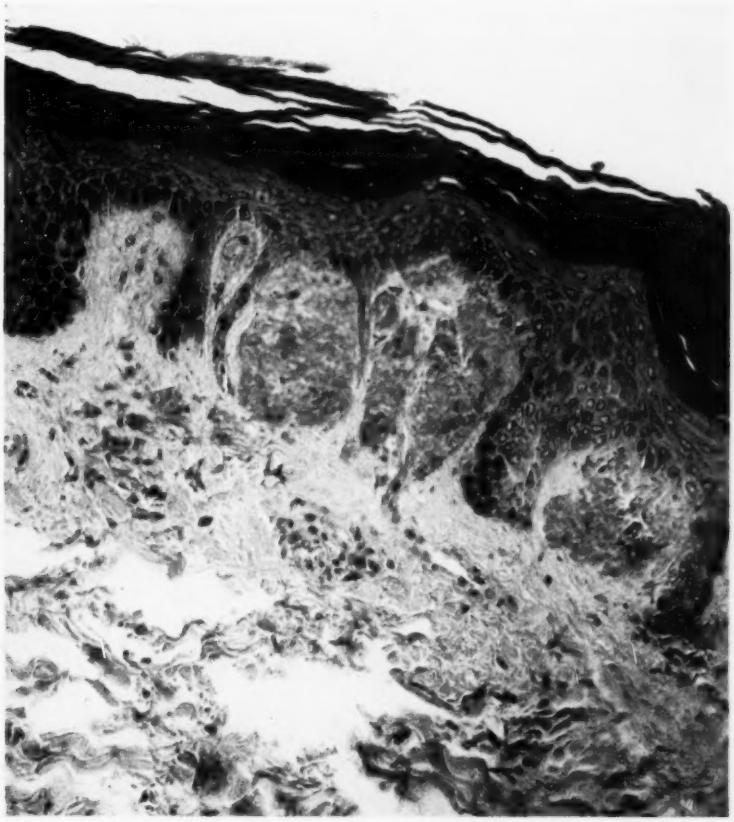

Fig. 3 (Case 1).—Methylrosaniline chloride stain of biopsy section, showing amyloid deposits in the papillary bodies easily differentiated from the contiguous collagen.

1927 who blocked the reticuloendothelial cells in animals and found that the deposit of amyloid was very much delayed in comparison with control animals.

Figure 3 demonstrates the traditional methylrosaniline chloride stain for amyloid which easily differentiates the amyloid from the contiguous collagen.

In 1942 Hass,[8] in chemical studies on the composition of amyloid, isolated a yield of 1.5% of acid polysaccharide from liver amyloid which he assumed was

7. Ebert, M. H., in discussion on Nomland, R.,[4b] p. 97.

8. Hass, G.: Isolation of Polysaccharide from Amyloid-Bearing Tissues, Arch. Path. **34**:92 (July) 1942.

chondroitin-sulfuric acid. Accordingly it occurred to us that the amyloid might react characteristically with the newer polysaccharide stains. The McManus method of staining [9] utilizes periodic acid and reduced fuchsin to detect polysaccharide substance in tissue. The periodic acid, according to Hotchkiss,[10] attacks substances with a 1, 2 glycol grouping or substituted aminos of alkylamino groupings. Aldehyde groups are formed which react with leucobasic fuchsin (Shiff's reagent) to give a red fuchsin stain. In case 1 specimens stained with the McManus method

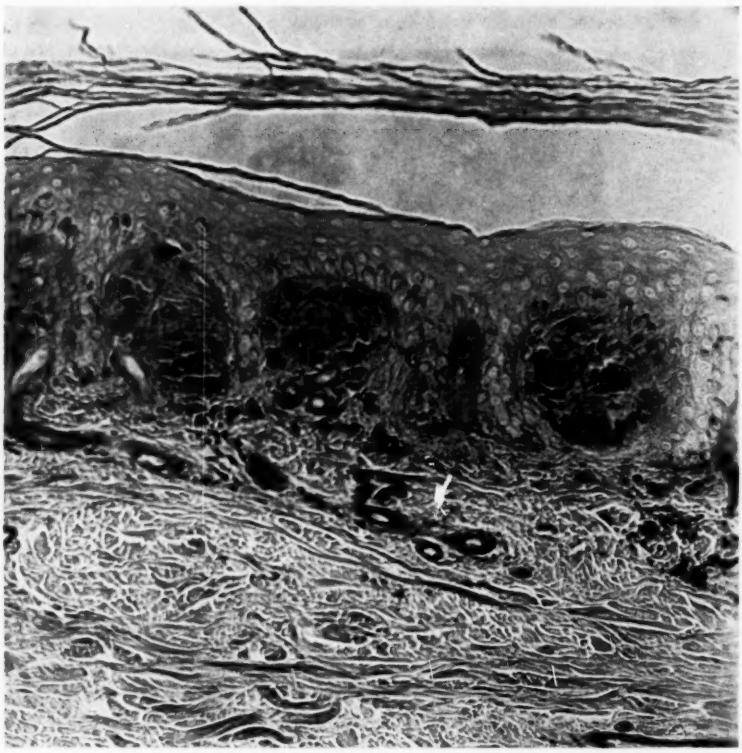

Fig. 4 (Case 1).—McManus stain of biopsy section. The darker areas directly under the epidermis represent the amyloid deposits, confirming the presence of polysaccharides in amyloid. The original color of the darker-staining material above is reddish-pink.

revealed that the amyloid deposits could be differentiated from collagen by the distinctive red color (Fig. 4).

The Hale stain [11] uses an acid solution of ferric hydroxide which combines with acid polysaccharides in tissue and stains blue when treated with hydrochloric acid

9. McManus, J. F. A.: Histological Demonstration of Mucin after Periodic Acid, Nature **158**:202 (Aug. 10) 1946.

10. Hotchkiss, R. D.: A Microchemical Reaction Resulting in the Staining of Polysaccharide Structures in Fixed Tissue Preparations, Arch. Biochem. **16**:131 (Jan.) 1948.

11. Hale, C. W.: Histochemical Demonstration of Acid Polysaccharides in Animal Tissues, Nature **157**:802 (June 15) 1946.

and potassium ferrocyanide. Recently Ritter and Oleson [12] have combined the McManus and Hale stains with a peroxidase stain of their own, and this combination was used to stain the amyloid in case 2 (Fig. 5). The amyloid deposits stand out very clearly as a deep blue, and amyloid can be seen surrounding some of the vessels deeper in the corium.

SUMMARY

1. Two cases are reported presenting a characteristic macular variant of amyloidosis cutis.

Fig. 5 (Case 2).—Black and white photograph of the Ritter-Oleson stain of biopsy section, demonstrating the amyloid deposits in the papillary bodies. The original color of these deposits is a deep blue.

2. Evidence is presented to show that amyloid reacts characteristically with polysaccharide stains, thus confirming previous reports of the presence of polysaccharide in amyloid. These stains also offer another histochemical approach to the detection and study of amyloid disease.

870 5th Ave. (21).

33 E. 70th St. (21).

12. Ritter, H. B., and Oleson, J. J.: Combined Histochemical Staining of Acid Polysaccharides and 1, 2 Glycol Groupings in Paraffin Sections of Rat Tissues, Am. J. Path. **26**:639 (July) 1950.

LOCALIZED ACQUIRED HYPERTRICHOSIS

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SAN ANTONIO, TEXAS
AND
THOMAS BUTTERWORTH, M.D.
READING, PA.

SINCE we have but meager knowledge of the factors influencing the growth of hair, and although the failure of hair growth creates greater popular interest, examples of hypertrichosis from any cause should be recorded in order to enhance our general information on the hair problem. With this in mind we are presenting a series of 13 patients in whom striking acquired localized hypertrichosis occurred as a result of prolonged, frequently repeated self-biting in the mentally deficient.

Hypertrichosis, excessive or abnormal growth of hair from any cause, may have local or general distribution and may be congenital or acquired. The most celebrated of the congenital hypertrichoses is the Russian "dog-faced" boy who was described by Jackson [1] in 1886. In this congenital type the affected person is born with generalized hypertrichosis. The excessive hair continues to grow after birth and increases in length and coarseness. Partial congenital hypertrichosis is fairly commonly observed, and it is usually associated with nevi. Localized excessive hair growth is seen in the lumbar and sacral region and is usually associated with spina bifida.

Permanent acquired hypertrichosis may be a manifestation of a number of organic diseases, such as benign and cancerous tumors of the adrenal cortex, anterior lobe of the pituitary, and ovary. Hirsutism in pregnancy, reported by Stoddard,[2] is probably associated with disturbance of the adrenal cortex.

In this presentation we are particularly concerned with partial or localized acquired hypertrichosis. Many of these conditions, such as the growth of hair on the chin and upper lip of normal women, defy explanation and lack apparent local and systemic causative factors. Hypertrichosis of malnutrition occurring on the legs of boys and girls also conceals its mechanism, though it disappears upon ingestion of an adequate diet. A mild prolonged irritative factor may be assumed to exist in hypertrichosis estivalis, a thickening and lengthening of the lanugo in the summer time. Also obscure in origin are partial or localized hypertrichoses which have been reported [3] as following accidents such as fractures and nerve injury. The presence

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1. Jackson, G. T., and McMurty, C. W.: A Treatise on Diseases of the Hair, Philadelphia, Lea & Febiger, 1912, p. 144.

2. Stoddard, F. J.: Hirsutism in Pregnancy, Am. J. Obst. & Gynec. **49**:417 (March) 1945.

3. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948, p. 1328.

of excessive hair on an extremity upon the removal of a cast is a frequent observation. This hypertrichosis is usually transient, and the hair falls as the injured part returns to normal function.

There remains a group of cases in which obvious cutaneous irritation has led to hypertrichosis. For instance, increased hair growth has occurred after local applications of plasters, liniments, and other irritant preparations. Goodman [4] observed that repeated applications of anthralin ointment caused increased pigmentation of the skin along with temporary increased hair growth. Becker [5] quoted Galewsky on the occurrence of localized hypertrichosis following temporary and prolonged cutaneous irritation by strong mercurial ointment or iodine tincture with subsequent wet dressings. On the other hand, a single injury to the skin may lead to increased hair growth, as in Becker's two cases [5] of acquired unilateral melanosis following severe solar dermatitis in which hypertrichosis of the pigmented areas later developed.

Repeated trauma to the skin involving friction and intermittent pressure is another cause of localized excessive hair growth. Csillag [6] in 1921 reported five cases of hypertrichosis in sack bearers. He found that over the areas of intermittent pressure on the shoulders and adjacent regions definite hypertrichosis developed. The same mechanism probably explains conditions seen by us in which an excessive amount of hair occurred about the peripheries of lichenified patches of neurodermite on the extensor surfaces of the forearms and on the thighs. Into this category also we place the series of cases presented in this paper. Prolonged intermittent biting of the hands or forearms in this group of patients has resulted in hyperkeratosis, pigmentation, and hypertrichosis of the traumatized sites.

When annoyed or tormented, patients with the lower grades of mental deficiency frequently bite themselves or others with a violent chewing motion. Among the 2,530 patients at the Pennhurst State School for the feebleminded, Spring City, Pa., in the summer of 1949, approximately 2% (53) indulged in this practice. These patients usually make a habit of biting the same area, most often the forearms, hands, and fingers, in that order. The skin in the area traumatized becomes erythematous, thickened, dry, hyperkeratotic, and frequently pigmented. In many instances a callous-like hardness occurs corresponding exactly with the pattern of the anterior teeth. In addition to these changes, in about 25% (13) of the "biters" an excessive growth of hair develops. It is such patients that form the subject matter of the present report.

Our material consisted of seven female and six male patients with localized acquired hypertrichosis. All of them were imbeciles or idiots. They ranged in age from 15 to 36 years, with most of them in the third decade of life. In only one instance could the amount of body hair be classified as excessive. In addition, 11 of the group showed excessive salivation. In one patient the saliva was excessively tenacious. As is common in low grades of mental deficiency, oral hygiene was poor in nine and only fair in four. In all cases the saliva gave an acid reaction to litmus.

4. Goodman, M. H.: Relation Between Pigmentation and Growth of Hair: Pigmentary Effects of Anthralin (Dihydroxyan-thranol) in 2 Cases of Alopecia Areata, Arch. Dermat. & Syph. **40**:76 (July) 1939.

5. Becker, S. W.: Concurrent Melanosis and Hypertrichosis in Distribution of Nevus Unius Lateris, Arch. Dermat. & Syph. **60**:155 (Aug.) 1949.

6. Csillag, J.: Note on Trade Hypertrichosis, Arch. Dermat. u. Syph. **134**:147, 1921.

The favorite biting site for 11 patients was the forearm, for 1 the wrist, and for 1 the dorsum of the hand. One patient was in the habit of biting both forearms, but in all others the traumatized area was unilateral. Eleven of the patients showed moderate to marked hypertrophy of the injured skin. The same number of patients exhibited increased pigmentation of varying degree, though there was no parallel between the occurrence of the discolorations and the thickness of the skin. In fact, one patient showed excessive hair growth without either hypertrophy or pigmentation, and two patients showed one change without the other.

Although it was obvious clinically that hypertrichosis was present at the traumatized sites, some quantitative estimate of the degree of change seemed desirable. Accordingly, a metal disk with a 1.0-cm. square opening was firmly taped in place. The hairs in the opening were then manually removed and counted. Corresponding sites on the opposite limb or areas close to the injured skin were chosen for the control tests. Three counts were performed in the traumatized area and a similar number in normal regions. The results were averaged. Representative hairs from

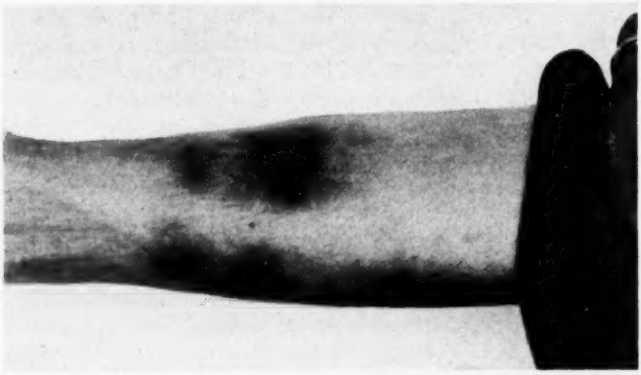

Fig. 1.—Four areas of pigmentation, hypertrophy, and hypertrichosis on the forearm from biting. The patient's upper and lower central incisors were missing.

each of the sites plucked were placed on scotch tape and measured. Although tedious and time consuming, we believe this technique to be accurate.

Using the method described, it was determined that the length of the hair and the number of hairs in the traumatized areas were substantially increased in comparison with control sites. The average number of hairs in the injured regions of the 13 patients was 32 per square centimeter as compared with 20.3 hairs in normal areas. In the patches of traumatized skin the average hair measured 20.5 mm. in length as against 13.0 mm. in comparable nontraumatized areas.

The pattern of the areas of hypertrichosis, pigmentation, and hypertrophy of the skin varies according to the technique of biting employed and the teeth of the patient. If the person uses a large bite, a familiar manifestation is skin changes on the anterolateral and posterolateral aspects of the forearm where irritated by the upper and lower teeth, with normal skin in between at the area of contact with the tongue. Loss of teeth modifies this pattern, as shown in Figure 1. This patient, D. V., exhibited four areas of pigmentation and hypertrophy arranged roughly in the form

of a square. Her upper and lower central incisors were missing, and this resulted in a nontraumatized area which presented an approximately normal appearance.

Some patients, on the other hand, used a much smaller bite, with the result that the area of noninvolvement at the region of contact with the tongue is much less conspicuous. C. P. (Fig. 2*A*) exemplifies this type of biter. She is also interesting in that both forearms were bitten, whereas unilateral involvement is the rule. Considerable hair growth occurred on both forearms, as shown in a side view of

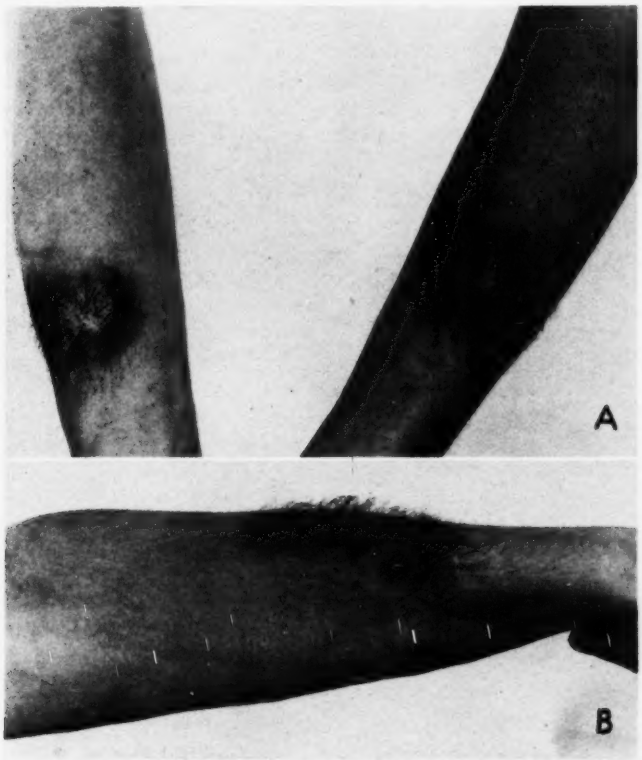

Fig. 2.—*A*, changes on both forearms as result of repeated biting. (Unilateral involvement is the rule.) *B*, side view of one of the lesions of same patient, emphasizing the increased hair length in the traumatized area.

one of them (Fig. 2*B*). In spite of sharp and jagged teeth, she never perforated the skin in her frequent paroxysms of biting.

A third group of patients may use a large bite in one region and a small one elsewhere. Figure 3*A* shows the forearm of one of the most frequent and persistent biters in the institution. Near the elbow she used a large bite resulting in the appearance of two hyperkeratotic pigmented areas of hypertrichosis separated by a zone of normal skin where the tongue rested. Lower down on the forearm there appears a diffuse pigmented hypertrophic pigmented plaque in an area every part of which was subject to the trauma of her teeth.

The hands responded to biting in a manner similar to the forearms. Figure 3*B* shows areas of pigmentation, hypertrophy, and increase in number and length of hairs in the irritated areas, while the central nontraumatized region is essentially normal.

Turning from the clinical to the histologic findings, microscopic examinations of the traumatized areas revealed a marked hyperkeratosis and acanthosis with the rete pegs extending to a uniform depth. There was a moderate perivascular lymphocytic cuffing. Increased pigmentation of the epidermis was noted but was

Fig. 3.—*A*, an extensive area of hypertrophy, pigmentation, and hypertrichosis due to biting. *B*, condition of a hand as a result of biting, showing that the hand responds in a manner similar to the forearm.

not marked. There was no evidence of increased mitotic proliferation or hypertrophy of the hair matrix and follicle which might indicate the possibility of the formation of new dermal papillae or hair follicles.

COMMENT

The increased hair growth as a result of biting reported herein apparently depends upon intermittent pressure associated with friction. The presence of saliva does not appear to be an important factor, for the areas most exposed to saliva,

namely those parts in contact with the tongue, fail to show changes in color, texture, or amount of hair. Suction likewise appears unimportant. Observation of mentally deficient biters for many years has convinced us that, in some patients at least, a definite sucking action is present. It would appear that the negative pressure would be greatest in the areas in contact with the tongue, but here the skin and hair remain normal.

Since histologic studies have failed to reveal evidence of the formation of new hair follicles or the activation of those long dormant, how do intermittent pressure and friction incite the growth of hair? We do not know but suspect that the constant trauma due to biting results in a hyperemia which stimulates hair growth. A clue is offered in the observation that most of the hair follicles in the abnormal areas contain two and sometimes three firmly attached hairs. One may postulate that under the influence of constantly repeated trauma, new hairs are formed immediately after the old hair becomes detached from the papillae. Delayed shedding of the old hair, possibly because of the hyperkeratosis present in most cases, with the simultaneous formation of new hair, may account for two or more hairs emerging from the same follicle and explain the increase in hair noted clinically.

SUMMARY

A series of 13 patients is presented showing a striking acquired localized hypertrichosis as a result of prolonged frequently repeated self-biting in the mentally deficient. There was a definite increase in hair length and number in the involved areas.

It is postulated that this increase in hair is due to hyperemia resulting from the continuous self-mutilation. The increase in the number of hairs is probably due to the delayed shedding of the old hair while new hairs are immediately formed, resulting in two or more hairs emerging from the same follicle.

Medical Arts Bldg.

411 Walnut St.

ASTEROL® DIHYDROCHLORIDE THERAPY OF MICROSPORUM AUDOUINI SCALP INFECTIONS

WILLIAM SNYDER, M.D.
PHILADELPHIA

WE HAVE been conducting clinical trials with several experimental preparations in the treatment of tinea capitis. In March, 1950, a study was begun with asterol® dihydrochloride. This antifungal material, the dihydrochloride of 2-dimethylamino-6-(*b*-diethylaminoethoxy)-benzothiazole, has been shown to be a potent fungicide both in vitro [1] and clinically,[2] with low sensitizing and low irritating properties. This report deals with those cases of Microsporum audouini scalp infection treated solely with a 5% asterol® dihydrochloride ointment in polyethylene glycol (carbowax®) 1500.

The areas of fluorescence under Wood's lamp were measured and charted on special forms, and mycological cultures were taken of infected hairs. The patients were instructed to shave or close-clip the scalp hair, to rub the medicament thoroughly twice daily into the entire scalp, and to shampoo the head nightly with medicinal soft soap liniment. A stocking cap, boiled and changed daily, was to be worn at all times. Patients were seen at weekly intervals for the first few weeks to detect any adverse reactions, then at two-week intervals.

Initially, 94 patients were treated, but only 60 are being reported since only these were able to be followed in detail. Forty-nine boys and eleven girls were observed for a period of 1 to 12 months. Of these, 31 were white, and 29 were Negro. Their ages ranged from 2 to 12 years, 72% being between 4 and 9 years old. Measurement of areas of fluorescence revealed diffuse generalized scalp involvement in 14, large or multiple patches in 26, a few small patches in 13, and localized infection in 7, usually on the occiput. All 60 patients showed M. audouini upon culture.

In 15 patients there was an irritation reaction at the site of application, characterized by erythema and micropapulation, and occasionally by tender kerion-like lesions. In 12 patients this reaction was manifested during the first month of ther-

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The asterol® dihydrochloride used in this study was furnished by Dr. R. J. Floody, Hoffmann-La Roche, Inc., Nutley, N. J.

From the Department of Dermatology and Syphilology, University of Cincinnati College of Medicine, Leon Goldman, M.D., Director.

1. Grunberg, E.; Soo-hoo, G.; Titsworth, E.; Ressetar, D., and Schnitzer, R. J.: Mycological Studies with a New Benzothiazole with Specific Activity Against Dermatophytes, Tr. N. Y. Acad. Sc. **13**:22 (Nov.) 1950. Reiss, F.: Antisporulating Effect of Asterol Dihydrochloride, ibid. **13**:28 (Nov.) 1950.

2. Stritzler, C.; Fishman, I. M., and Laurens, S.: Treatment of Tinea Capitis with a New Antifungal Compound: Preliminary Report, A. M. A. Arch. Dermat. & Syph. **63**:606 (May) 1951.

apy; in 3 patients it occurred in two to three months. The reactions subsided in one to three weeks upon discontinuing the medication and applying boric acid wet dressings. After that, continued medication with asterol® dihydrochloride was tolerated with no further irritation. In one patient with irritation secondary impetiginization of the scalp developed from which a penicillin-resistant Micrococcus pyogenes aureus was cultured. The pyogenic infection responded to terramycin administered orally, and then the fungicide was reapplied.

Of the 60 treated patients, 24 remained unchanged, 21 showed some decrease in the extent and/or severity of the infection, and 15 showed clinical and cultural cures within 1 to 10 months. Of the cures, 11 were achieved within the first five months. Biweekly postcure observations were made for one to seven months, with no relapses noted. Only three cures occurred among the group of patients showing irritation reactions. Of the remaining 12 patients with irritation, 8 showed no change in the ringworm infection, and in 4 a decrease of fluorescence resulted.

In our experience, asterol® dihydrochloride has been superior in results to other fungicides which we have employed in M. audouini scalp infections. Although the percentage of cures in this series is generally lower than that obtained by other observers,[2] this controlled study used no accessory therapeutic aids, such as manual epilation, which increase the rate of cure.[3] Also, the inflammatory reactions in our patients were mostly of a mild character and did not produce a greater tendency to cure the ringworm infection, as is commonly experienced in true kerion.[4]

CONCLUSIONS

Ninety-four patients with Microsporum audouini infection of the scalp were treated with 5% asterol® dihydrochloride ointment, but only 60 cases were followed in detail and are reported. Cures were observed in 15 patients (25.0%), improvement in 21 (35.0%), and no change in 24. Temporary scalp irritation developed in 15 patients. In only three patients did this inflammatory reaction possibly exert a beneficial effect of curing the ringworm infection. Asterol® dihydrochloride appears to be an effective antifungal agent in tinea capitis.

804 Pine St. (7).

Dr. S. S. Schwebel assisted in the initial phase of this study.

3. Wilson, J. F.: Manual Epilation in Treatment of Tinea Capitis, Arch. Dermat. & Syph. **60**:347 (Sept.) 1949.

4. Scully, J. P.; Livingood, C. S., and Pillsbury, D. M.: The Local Treatment of Tinea Capitis Due to M. Audouini: The Importance of Inflammatory Reaction as an Index of Curability, J. Invest. Dermat. **10**:111 (March) 1948. Kligman, A. M., and Anderson, W. W.: Evaluation of Current Methods for the Local Treatment of Tinea Capitis, ibid. **16**:155 (March) 1951.

ACCIDENTAL TATTOOING OF THE FACE TREATED BY ABRASION WITH SANDPAPER

WILLIAM A. ROSENBERG, M.D.
CHICAGO

TREATMENT of accidental tattooing heretofore has been most unsatisfactory. Various chemical methods have been employed. In 1888, Variot [1] advocated tattooing a concentrated solution of tannin into the mark, followed by immediately rubbing a silver nitrate stick over the treated area. The part thus treated blackens, and a crust forms and drops off, leaving a fine scar. Various modifications of this method have been described. Shie [2] employed a tattooing instrument and a 50% solution of tannic acid. Lerner [3] used superficial cross-hatched scarifications through a lake of 10% aqueous tannic acid solution. Brault [4] tattooed a solution of 75% zinc chloride into the mark. Karpelis [5] cross hatched the skin deeply with a fine scalpel and rubbed in potassium permanganate. In cases of argyria, Stillians and Lawless [6] employed intradermal injections of a mixture of 6% potassium ferrocyanide. Treatment by mechanical abrasion, such as rubbing the tattoo mark with pumice stone, has been employed with varying results. Janson [7] rubbed the tattooed area with a stiff brush until bleeding was produced. Frequent repetition of this therapy was necessary to produce desirable results. Tulipan,[8] in discussing Lerner's paper, stated that whether one uses mechanical means, electrolysis, coagulation current, scarification, carbon dioxide snow, or chemicals, the rationale in all these methods in the same, i. e., the production of a superficial destruction of the skin with resulting scar formation.

Recently I treated an accidental blue tattooing of the face by abrasion with sandpaper. Since the result was good, leaving no scarring, and since I find no reference in the literature to this form of therapy, I thought it advisable to make this preliminary report.

From the Department of Dermatology and Syphilology, Chicago Medical School.

1. Variot, G.: Nouveau procédé de destruction des tatouages, Compt. rend. Soc. biol. **5**:636 (July) 1888.

2. Shie, M. D.: A Study of Tattooing and Methods of Its Removal, J. A. M. A. **90**:94-99 (Jan. 14) 1928.

3. Lerner, C.: Removal of Tattoo Marks, New York J. Med. **48**:1937-1939 (Sept. 1, Pt. 1) 1948.

4. Brault, J.: Ablation des tatouages par les piqûres serrees au chlorure de zinc, application de la méthode à la querison des naevi, Ann. dermat. et syph. **6**:33, 1895.

5. Karpelis, E.: Über Entfernung von Tatauierungen, Münch. med. Wchnschr. **84**:529-530 (April 2) 1937.

6. Stillians, A. W., and Lawless, T. K.: Intracutaneous Method of Treating Argyria, Arch. Dermat. & Syph. **17**:153-155 (Feb.) 1928.

7. Janson, P.: Eine einfache Methode der Entfernung von Tatauierungen, Dermat. Wchnschr. **101**:894-895 (July 20) 1935.

8. Tulipan, L., in discussion on Lerner.[3]

Fig. 1.—Accidental tattooing of the face before treatment.

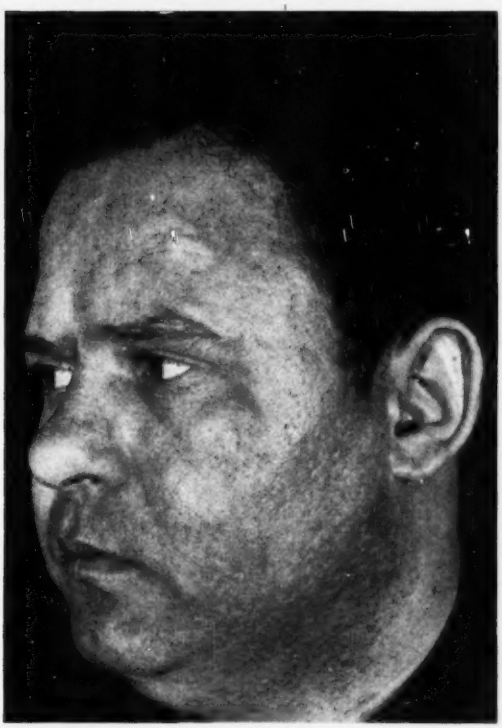

Fig. 2.—Accidental tattooing of the face after treatment.

REPORT OF THE CASE

J. J., a 35-year-old white man, a truck driver, was first seen May 4, 1950, for a bluish tattooing of the face (Fig. 1). He stated that the disfigurement had been caused about seven months before by an explosion of the gas tank of his truck while he was checking it. Examination showed bluish tattoo marks consisting of streaks and discrete bluish pigmented spots and patches on the left side of the face, especially involving the left side of the forehead and the

Fig. 3.—Photomicrograph showing brownish-black pigmented masses in the midcorium; hematoxylin and eosin; × 100.

infraorbital region. As a result, his co-workers frequently teased him for having a black-and-blue eye.

On May 18, 1950, an area about 2.5 cm. on the left cheek was anesthetized with procaine hydrochloride, and the skin over the area was treated by abrasion with sandpaper, grit No. 3/0, until bleeding was profuse. Within 48 hours a crust formed which fell off in about five days leaving a smooth pink surface. In about 10 to 14 days the area healed. Similarly involved areas were likewise treated at weekly or biweekly intervals.

Some particles removed from the skin were submitted to M. M. Platte, metallurgist, for chemical analysis and proved to be type 1010 steel, having the following content:

	Per Cent
Iron	99.00
Carbon	0.09
Sulfur	0.024
Phosphorus	0.003
Silicon	0.02
Manganese	0.36
Residual	0.5

Fig. 4.—Photomicrograph showing blue-stained masses of iron-containing pigment; hydrochloric acid and potassium ferrocyanide (Perls' test); × 100.

On Feb. 21, 1951, two months after the last treatment, the case was presented before the Chicago Dermatological Society. Examination at that time showed excellent results and no cicatrization (Fig. 2).

HISTOPATHOLOGIC REPORT

A biopsy of the left cheek showed the horny layer to be thinner than normal, with no evidence of parakeratosis. The granular layer varied in thickness and was present throughout the section. There was a moderate acanthosis and edema of the prickle cells. In one localized area the epidermis and a portion of the corium were absent. In the papillae the blood vessels were dilated, and there was a round-cell infiltrate.

In the midcorium and extending from the subpapillary layer to the level of the sweat glands there were circumscribed masses of cellular infiltrate (Fig. 3). Each of these inclosed considerable dark pigment of a yellow to brownish-black hue. Staining with hydrochloric acid and potassium ferrocyanide (Perls's test) showed blue-stained masses of iron-containing pigment (Fig. 4). The hair follicles, sebaceous glands, and sweat glands showed no pathologic changes.

SUMMARY

A case of accidental tattooing of the face is reported which was successfully treated by abrasion with sandpaper. The disfigurement was removed, leaving no residual cicatrization.

185 N. Wabash Ave.

LINEAR UNILATERAL BASAL-CELL NEVUS WITH COMEDONES

Report of a Case

ROBERT G. CARNEY, M.D.
IOWA CITY

ALTHOUGH nevi have been the subject of a great many papers, much interest, and many philosophical arguments since the earliest days of medicine, it appears that there are still "new" nevi which have escaped detection and description in the past. I have recently studied a singular case of the nevus-unius-lateralis type which proved to be a systematized basal-cell nevus.

REPORT OF CASE

O. J., a 69-year-old white man, was seen in the department of dermatology and syphilology of the University Hospitals on May 16, 1951, on referral from the department of surgery, where he was being treated for an adenocarcinoma of the colon. He was a small, emaciated man with a marked congenital dorsal scoliosis and peculiar smooth growths on the skin of the left side of the body, also present since birth.

Examination of the skin showed bands of varying width on the left side of the chest (Fig. 1*A*) and abdomen, limited medially by the midline. There were narrow bands extending down the anterior surface of the left arm, down the anteromedial aspect of the left thigh, down the posterior aspect of the left thigh, and continuing down the posteromedial surface of the leg halfway to the ankle. A wider band extended upward over the left occipital scalp area, anteriorly over the left parietal area, and then downward to the left cheek anterior to the ear. Each of these bands was made up of two elements, clinically distinct but completely intermingled (Fig. 1*B*): first, blackheads of variable size and in no way distinguishable from ordinary comedones or particularly from those seen in nevus unilateralis comedonicus, and second, smooth globular papules and small tumors from 2 to 10 mm. in diameter. Of the latter, the smaller were clear and somewhat vesicular or pearly in appearance, while the larger were light-brown. The comedones and tumors were discrete, in some areas being sparsely scattered in the band-like distribution, and in other portions, closely set; at some points they formed narrow lines within the bands.

At the base of the neck on the left shoulder there was a 5-mm. ulcer with a rolled, pearly border; anterior to the left ear were two similar ulcers, 5 and 10 mm. in diameter. All of these lesions were within the bands of nevoid change, and all were clinically typical basal-cell epitheliomas; their duration was unknown to the patient. Other physical findings included epicanthus of the left lid and a marked dorsal scoliosis to the left with attendant thoracic deformity.

Tissue was removed from three different areas of mixed comedones and tumors, from a single comedo, and from two of the three epitheliomas; all six of these biopsy specimens showed similar basal-cell newgrowth. The single large comedo represented a pear-shaped invagination of thin epidermis from three to four cells thick (Fig. 2*A*). The lumen was filled with keratinized material and cellular debris. The dermis around and beneath the invaginated epidermis contained masses of basal-type cells in solid strands and "islands," each three to five cells thick (Fig. 2*B*). There were one or two small keratinized cysts within the strands of basal cells. There were several relatively normal-appearing sweat glands nearby, and the rest of the dermis was normal.

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Sections of the small tumors showed essentially the same picture (Fig. 2C). Some of the nodules were made up of solid strands of basal-type cells and occasional small keratinized cysts. Others, especially the larger ones, also contained large cysts similar to the comedones, except that they did not have an orifice. One of the large nodules showed interconnecting strands of basal cells enclosing clear, nonkeratinized spaces, a structure frequently seen in cystic basal-cell epitheliomas. Most of the basal-cell masses were in the upper third of the dermis, but here and there similar collections appeared deep in the pars reticularis.

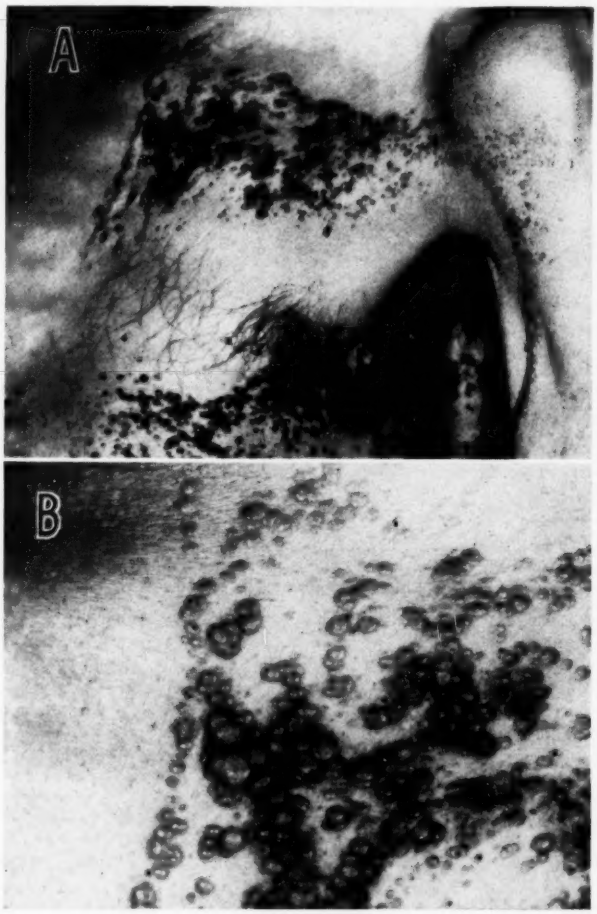

Fig. 1.—*A*, linear arrangement of the nevus on the trunk and upper arm. *B*, close-up of upper chest showing both globular tumors and comedones.

In the biopsy specimens from the frankly epitheliomatous lesions on the cheek a multiplicity of variations in basal-cell epithelioma were observed (Fig. 2D). Parts of both epitheliomas were exactly the same in structure as the nevus. Contiguous areas showed larger strands made up of somewhat more eosinophilic and more fusiform cells, while other areas showed large lobulated solid masses of basal cells, and still another showed a latticework of basal cells in interconnecting strands separating clear cystic spaces. Numerous mitoses were visible in most of the epitheliomatous tissue.

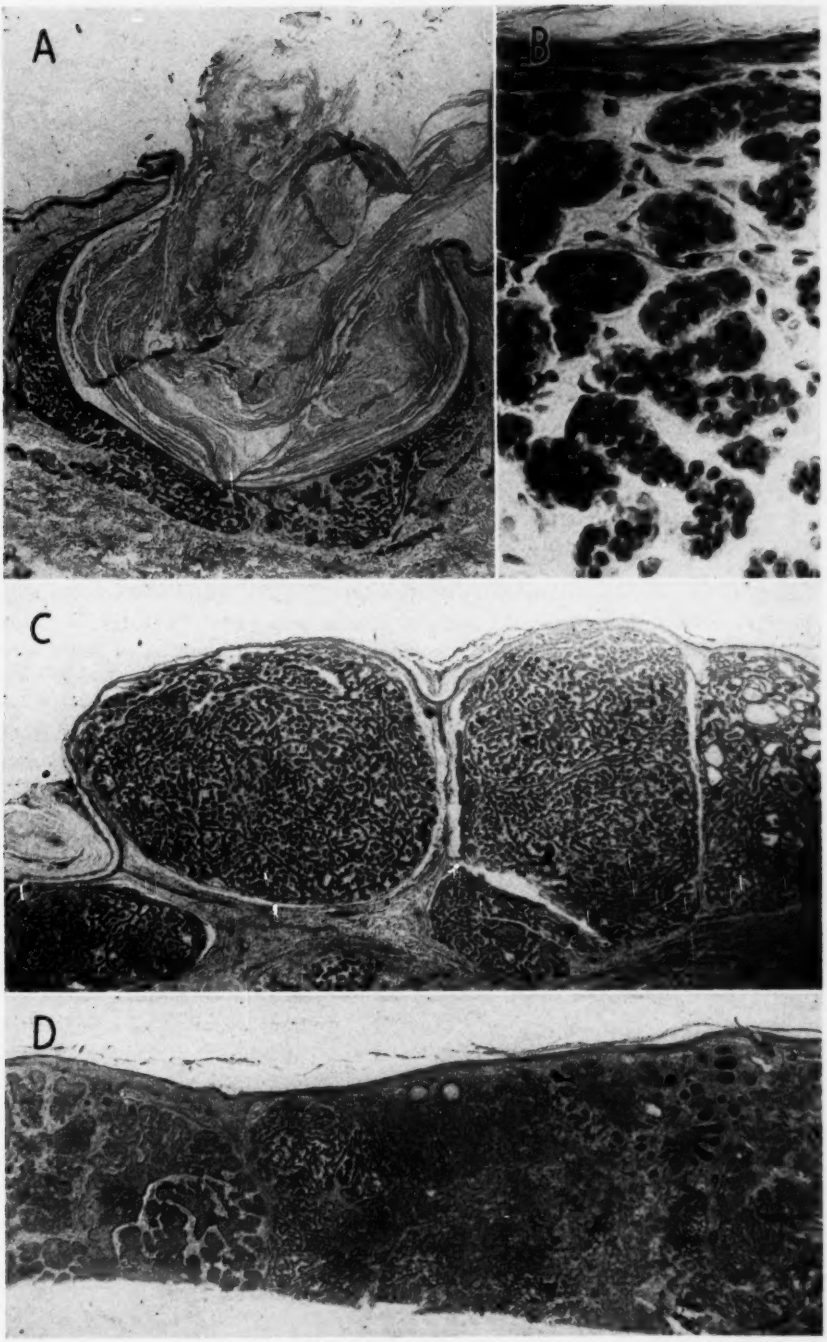

Fig. 2.—*A*, section through comedo-like lesion showing thin-walled, keratinized pit surrounded by basal-cell nevus; low-power magnification. *B*, section through wall of comedo in *A*; high magnification. *C*, section through a globular tumor from chest wall showing basal cells in masses of solid strands, left and center, and in cystic arrangement at right; low-power magnification. *D*, section through basal-cell epithelioma from left cheek showing several variations in the architecture of the neoplasm; low-power magnification.

COMMENT

The word "nevus," in its broadest sense, can be applied to a great number and wide variety of new growths, anomalies, and hamartomas; indeed, it is a word almost impossible to define. Nevi may be composed of collections of nevus cells or of dermal melanoblasts; they may be epithelial, of verrucous or ichthyosiform character. Other forms of nevi may be composed of vascular tissue, connective tissue, fat, nerve components, sweat and sebaceous glands and perhaps anomalies thereof, hair, comedones, and a variety of epidermal elements. By Jadassohn's [1] definition the word "nevus" may also denote a lack of elements normally present, nevus anemicus and nevus depigmentosus being examples. The distribution of nevi also varies, from solitary and scattered moles to types which are symmetrically grouped, as on the face, and to types which are unilaterally and bilaterally systematized or linear in arrangement. Only in a few types is there persistent correlation between the distribution pattern and the cellular components of nevi; most of the possible variations seem to have been reported at one time or another. In this study the primary interest is in nevi of linear distribution and those composed of epidermal elements.

Linear nevi were first described by Bärensprung [2] in 1863 in his report of a case of nevus verrucosus unius lateris s. linearis. Since that time many linear nevi have been reported, and with a variety of cellular components. In addition to the linear warty epithelial nevi, there are some which consist of pigmented macules or lentigines in lines and bands, while others are composed of bands of soft flat papules, the so-called nevus spilus. MacKee,[3] in 1913, presented a patient with an extensive linear and unilateral lack of pigment. Hemangiomatous and lymphangiomatous linear nevi are occasionally seen. Nevus unilateralis comedonicus has been repeatedly described, consisting of large comedones arranged in linear form and usually complicated by acne and postacne scarring. Most of the reported cases [4] of blackhead nevi show no hypertrophy of the sebaceous glands, and in fact show only invaginated, keratinized pits with no connection with sebaceous glands. Pinkus [5] presented four cases of nevus unilateralis comedonicus in 1907; case 3 was reported to show a great hypertrophy of the sebaceous glands.

Glandular and other epidermal nevi have also been described in a great number of forms. Sebaceous gland nevi are relatively common. Sweat gland nevi in their

1. Jadassohn, J.: Dermatologie, ed. 2, Vienna, Verlag für Medezin, Weidmann & Co., 1938, p. 427-436.

2. Bärensprung, cited by Josef, M. in Mraček, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1904, Vol. 3, p. 547.

3. MacKee, G. M.: Nevus Unius Lateris, J. Cutan. Dis. **31**:1038, 1913.

4. Kofmann, S.: Ein Fall von seltener Lokalization und Verbreitung von Komedonen, Arch. Dermat. u. Syph. **32**:177, 1895. Selhorst, S. B.: Nevus Acneiformis Unilateralis, Brit. J. Dermat. **8**:419 (Nov.) 1896. Thibierge, G.: Nevus Acneiformis Unilateralis, Ann. dermat. et syph. **7**:1298, 1896. Bettmann: Über den Naevus acneiformis, Arch. Dermat. u. Syph. **80**:63, 1906. White, C. J.: Nevus Follicularis Keratosus, J. Cutan. Dis. **32**:187, 1914. Hodara, M.: Histologische Untersuchung eines klinisch hauptsächlich in Form von Komedonenlinien zeigenden Falles von Naevus unilateralis comedo-follicularis, Arch. Dermat. u. Syph. **123**:409, 1916. Klein, A.: Über einen halbseitigen systematisierten Naevus follicularis keratosus, ibid. **124**:571, 1917. Senear, F. E. and Perlstein, M. O.: Nevus Unilateralis Comedonicus, Arch. Dermat. & Syph. **32**:680 (Oct.) 1935.

5. Pinkus: Naevus acneiformis, Arch. Dermat. u. Syph. **88**:354, 1907.

true form are much more unusual, cases having been reported by Petersen,[6] Beier,[7] and Paviot.[8] Arnold[9] has reported a mixed nevus showing hypertrophy of both sudoriparous and sebaceous elements. Whether such cystic lesions as steatomatosis can be considered nevi is debatable. There is more reason to so consider the syringoma, the cylindroma, and the multiple benign cystic epithelioma. These are said to be of sweat-gland or hair-follicle origin, such deductions being largely based on contiguity and morphologic similarity. Hairy nevi are very common, often in a mixture with other nevus elements. In 1914 Adamson[10] reported a case of a nevus of the eyelid which was histologically indistinguishable from a basal-cell epithelioma, and Nomland[11] in 1932 reported a case of multiple pigmented basal-cell nevi, some of which underwent malignant change and became frank basal-cell epitheliomas.

Certain of these nevi with epidermal cellular elements occur in unilateral linear fashion, but most of them only infrequently. Linear nevi of the verrucosus, spilus, pigmentosus and comedonicus types have already been mentioned. Sebaceous gland nevi commonly occur in linear form. Leven,[12] for example, reported a rather extensive one in 1930. Petersen,[6] in 1892, reported a unilateral linear nevus which was made up clinically of smooth and warty nodules, but which microscopically proved to be made up of large coil glands, ducts lined with columnar and cuboidal cells, and solid epidermal strands. His description and pictures show no similarity to syringoma, epithelioma adenoides cysticum, or nevus syringocystadenomatosis papilliferus. Dorst and Delbanco[13] published a preliminary report in 1901 concerning a linear nevus apparently made up of mixed elements, partly sebaceous glands and partly what resembled epithelioma adenoides cysticum microscopically. The promised complete report, including illustrations of the microscopic picture, apparently never materialized. A case of nevus syringocystadenomatosis papilliferus in a linear, unilateral distribution on the head, neck, shoulder, and chest was reported in 1904 by Kreibich.[14]

The case most nearly like the one reported here, at least in its histological appearance, was presented at the meeting of the Chicago Dermatological Society,

6. Petersen, W.: Ein Fall von multiplen Knäueldrüsengeschwülsten unter dem Bilde eines Nävus verrucosus unius lateris, Arch. Dermat. u. Syph. **24**:919, 1892; Beiträge zur Kenntniss der Schweissdrüsen-Erkrankungen, ibid. **25**:442, 1893.

7. Beier, E.: Über einen Fall von Naevus subcutaneous (Virchow) mit hochgradiger Hyperplasie der Knäueldrüsen, Arch. Dermat. u. Syph. **31**:337, 1895.

8. Paviot, cited by Josef, M. in Mraček, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1904, Vol. 3, p. 558.

9. Arnold, H.: Nevus Seborrheicus et Sudoriferus, Arch. Dermat. & Syph. **51**:370-372 (June) 1945.

10. Adamson, H. G.: On the Nature of Rodent Ulcer; Its Relationship to Epithelioma Adenoides Cysticum of Brooke and to Other Trichoepitheliomata of Benign Naevoid Character; Its Distinction from Malignant Carcinoma, Lancet **1**:810, 1914.

11. Nomland, R.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. **25**:1002-1008 (June) 1932.

12. Leven: Systematisierter Naevus sebaceus bei gleichzeitigem Vorhandensein einer Ptosis, Dermat. Wchnschr. **91**:1440-1442, 1930.

13. Dorst and Delbanco: Zur Anatomie der strichförmig angeordneten Geschwülste der Haut, Monatsschr. prakt. Dermat. **33**:317, 1901.

14. Kreibich, K.: Ein Fall von Adenoma folliculare cutis papilliferum, Arch. Dermat. u. Syph. **70**:3, 1904.

Feb. 15, 1950, by Rodin.[15] This case was clinically diagnosed neurofibromatosis, presenting clear globular tumors and light-brown pedunculated growths on the trunk, neck, and eyelids; there were no café-au-lait spots, nor was there any systematized arrangement. Microscopic studies proved these tumors to be epithelial newgrowths resembling basal-cell epitheliomas, and Caro[16] classed the case as one of multiple basal-cell nevi or hamartomas. Examination of the borrowed sections showed a structure even more like the classic basal-cell epithelioma than ours which tended toward an architecture suggesting abortive adenoid and tubular growth.

Our case, therefore, appears to be unique in the literature on nevi not only in the linear and unilateral distribution of a basal-cell nevus but in the presence of clinical comedones which proved to be keratinized epidermal pits in conjunction with the same basal-cell-nevus elements found in the nodular portions of the nevus. In three areas, all within the bands of nevoid growth, clinically and histologically malignant basal-cell epitheliomas were present, presumably having arisen from the nevus itself. The adenocarcinoma of the colon was considered to be an unrelated condition; there was no adequate study of the rest of the bowel mucosa, and if anomalous changes also occurred there, they were not discovered. As frequently occurs in nevoid disorders, other congenital defects were present in this patient.

The question of more precise classification of the type of cell present in this nevus has studiously been avoided. Contiguity and structurally similar morphology are not adequate guides to the origin of epithelial newgrowths, although these features invite interesting conjecture. Whether this nevus is of basal-cell origin, or from sweat glands or hair follicles, cannot be proved. Since the glands and follicles develop from the epidermis by downward proliferation, there is no reason why a basal-cell nevus or a basal-cell epithelioma may not revert to the ontogenetically ancestral cell type and thus develop a morphology more or less resembling one of these daughter structures. Equally, there is no reason why a nevus or epithelioma might not develop from a sweat gland, either during its development or later in life, as the case may be. The question is one which may never be solved.

SUMMARY

A unique case of unilateral, linear, systematized nevus is reported. Clinically the nevus was made up of smooth, rounded, clear to light-brown nodules interspersed with comedones, but histologically all of the nevus proved to be a basal-cell nevus. At three points in the nevus true basal-cell epitheliomas had developed.

University Hospitals.

15. Rodin, H. H.: Neurofibromatosis, Arch. Dermat. & Syph. **63**:530 (April) 1951.

16. Caro, M. R., in discussion on Rodin.[15]

GENETIC STUDY OF HEREDITARY TYPE OF EPIDERMOLYSIS BULLOSA SIMPLEX

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AT ONE time epidermolysis bullosa was considered a comparatively rare disease. During World War II, however, appreciable numbers of persons with this dermatosis were found among those inducted. Many of these patients reported that other members of their families were similarly affected, and thereby some interest was aroused regarding the manner of inheritance. A number of reports on the subject, from both the clinical and the genetic point of view, have been published since 1940. Only the report by Johnson and Test [1] in 1946 represents an extensive genetic study. The progenitor of the larger of the two families reported by them came from Ireland about 1770. Since certain members of the family herein reported descended from Irish immigrants about the same time, it seemed pertinent to investigate this Alabama family for a possible familial connection with those of Johnson and Test.

From previous reports it is readily noted that epidermolysis bullosa covers a group of similar dermatoses with varying clinical and genetic features. There are two major divisions, namely, the simple and the dystrophic varieties (Table). The present report concerns one of the simple, nondystrophic types. Among the simplex types there have been reported patients with and without familial history of the disease. If a familial history was obtained, the affected persons were found to have been involved according to a simple Mendelian dominant trait. In some the lesions have been limited to the feet or the feet and hands; in others the lesions may have been more generally distributed. Features common to most of this group have included local production of bullae following trauma, healing without scar formation, and tendency toward increased bullae formation during hot weather.

Among the members of the family herein reported, the bullae most often appeared first on the knees, feet, and hands, and usually in infancy at the time the

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Read at the Seventy-First Annual Meeting of the American Dermatological Association, Hot Springs, Va., May 23, 1951.

From the Department of Dermatology and Syphilology, Medical College of Alabama (Dr. Noojin and Dr. Croom), and the Department of Zoology, Florida State University (Dr. Reynolds).

1. Johnson, S. A. M., and Test, A. R.: Epidermolysis Bullosa Simplex of the Hands and Feet, Arch. Dermat. & Syph. **53**:610-619 (June) 1946.

child first began to crawl. In this family, if the dermatosis had not appeared by the end of the first year of life, subsequent development of the disease was unlikely. The severity of the disease varied slightly from one person to another. Involvement appeared to be less severe as the child became older; however, the period at or near puberty did not appear to alter the clinical course appreciably. Improvement with age may have been due, in part, to the fact that the more mature persons had learned to cope with the situation and were more cautious. The bullae were more

Important Varieties of Epidermolysis Bullosa

I. Simplex varieties
  a. Dominant forms
    1. Feet only
    2. Hands and feet
    3. Generalized
  b. Acquired forms
II. Dystrophic varieties
  a. Dominant form
  b. Recessive form
  c. Guy's type
  d. Wende's type
  e. Macular type
  f. Epidermolysis bullosa hereditaria letalis

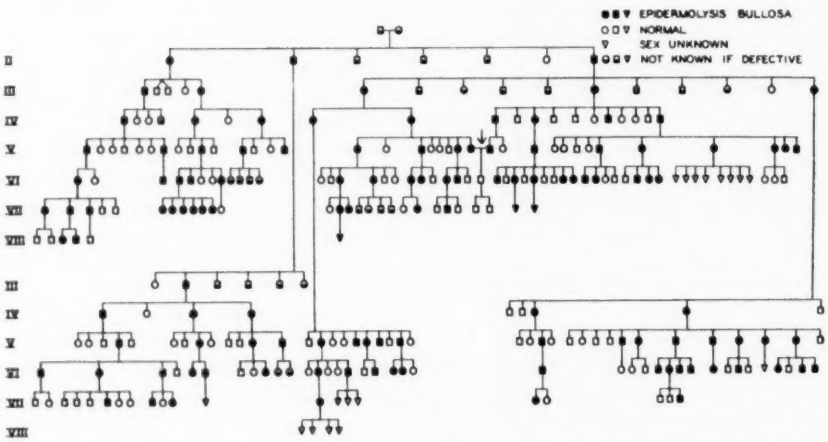


Fig. 1.—Incidence of epidermolysis bullosa simplex in a family in which most of living members now reside in Alabama; arrow indicates only reported marriage in which both parents were affected.

prominent on the hands and feet, but often occurred on any part of the body subjected to irritation. Oral lesions were noted infrequently. Bullae were noted often on the shoulders, neck, and at the waist line, where contact irritation was more likely to be produced by clothing. Loss of nails occurred occasionally. Residual scarring, hyperhidrosis, dermographia, and hemorrhagic bullae usually did not occur.

Figure 1 shows the incidence of epidermolysis bullosa simplex in a family whose living members, for the most part, now reside in Alabama. The second generation of this family, consisting of two affected brothers and two sisters, one

of whom was also affected, migrated from South Carolina to Alabama during the first two decades of the 19th century. Some of the members of other similar families came to Alabama by way of Kentucky and Tennessee, while still others had short sojourns in Georgia.

It will be observed in Figure 2 that of 242 descendents in families in which one parent was known to have epidermolysis bullosa and all siblings were known to be either affected or normal, 114 were affected and 128 were normal. With the application of the chi-square test, a chi-square value of 0.8098 is obtained, indicating an insignificant deviation from a 1 to 1 ratio. This ratio would be expected if the trait were dependent upon a simple dominant factor, and therefore, supports the conclusions of Cartledge and Myer,[2] Mansur,[3] and Johnson and Test.[1]

The 283 persons included in Figure 1 represent only those persons affected with epidermolysis and their immediate offspring. For the sake of simplicity descendents of the normal siblings represented in Figure 1 are not shown. Two hundred and eighty of these descendents are known to us, and, unless they married affected cousins, not one case of epidermolysis bullosa appeared among them.

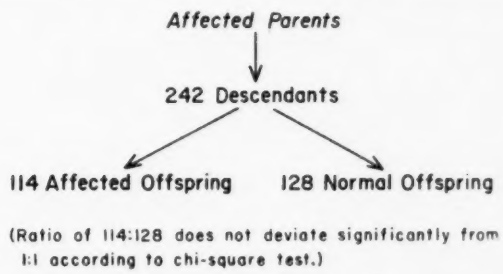

Affected Parents
242 Descendants
114 Affected Offspring
128 Normal Offspring
(Ratio of 114:128 does not deviate significantly from 1:1 according to chi-square test.)

Fig. 2.—Disease incidence. A 1 : 1 ratio would be expected if the trait were dependent upon a simple dominant factor.

This was to be expected if the simple-dominant-factor hypothesis were correct. One of the normal male twins in the third generation married his affected first cousin, the oldest daughter of his younger affected uncle (Figure 3). They had two affected daughters. After her death he married a normal, unrelated woman by whom he had 7 normal children and more than 90 descendents beyond the first generation, all of whom were normal. The twin brother was equally prolific, and no case of epidermolysis bullosa has appeared among his descendents.

Previous reports have frequently suggested that consanguinity may be responsible for a homozygous condition of a recessive factor upon which the disease might be dependent. In the Alabama family two marriages of second cousins took place in which the four persons were normal, and both families had affected siblings (Figure 4). Both of these couples had many offspring with no occurrence of epidermolysis bullosa. Two other second cousin marriages occurred of which one member of each pair was affected. In both of the latter cases some of the resulting

2. Cartledge, J. L., and Myer, V. W.: Inherited Foot-Blistering in an American Family, J. Hered. **34**:24 (Jan.) 1943.

3. Mansur, H. D., Jr.: Hereditary Epidermolysis Bullosa, J. A. M. A. **120**:1122-1124 (Dec. 5) 1942.

offspring were affected, as would be expected without consanguinity. In view of these data it would appear that consanguinity is insignificant in the transmission of this type of epidermolysis bullosa.

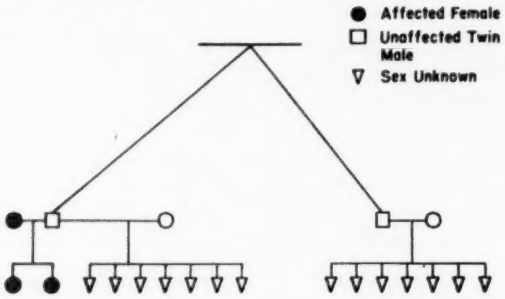


Fig. 3.—Marriages of normal male twins. One married an unaffected woman; the other married an affected woman and later an unaffected woman. The offspring of these marriages are shown.

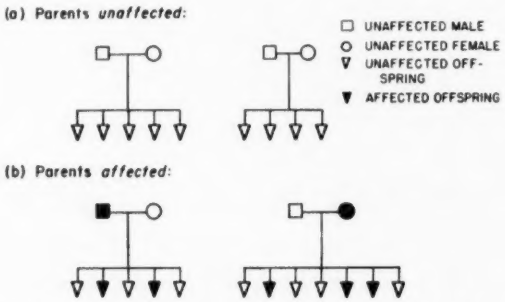
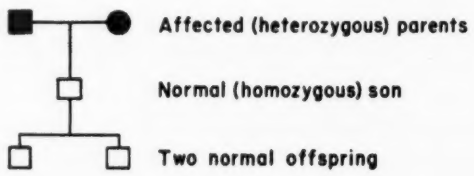


Fig. 4.—Two marriages of second cousins, all of whom were unaffected but had affected siblings, had many offspring with no occurrence of epidermolysis bullosa. Two other second cousin marriages occurred of which one member of each pair was affected. In both of the latter cases some of the resulting offspring were affected, as would be expected without consanguinity.



(A *simple dominant factor* must be responsible.)

Fig. 5.—Marriage of two affected persons produced an unaffected son who had two unaffected children.

Heretofore no family has been reported in which both parents were affected. Within this family two affected persons married each other (Figures 1 and 5). One homozygous normal son, now the father of two normal children, was born to these two heterozygous parents. This would seem to be final evidence that a simple dominant factor is responsible for this variety of epidermolysis bullosa simplex.

There seems to be no evidence in our data for any sex-related phenomena of inheritance of the disease. Of the 117 affected persons, 52 were males and 65 were females (Figure 6). Contrary to Greenberg's [4] findings, men and women alike transmit the factor and transmit it approximately equally to male and female offspring. Fathers have transmitted it to 48 offspring and mothers to 61.

So far no familial connection has been found between the family herein reported and those reported by Johnson and Test. The latter included families reported by Cartledge and Myer and Mansur. Thompson, Leedham, and Hailey [5] reported one small family from northern Alabama in which epidermolysis bullosa hereditaria occurred through five generations. Their family was not included in ours, but it would not be surprising to discover a familial connection between the two. Nothing is known regarding the descendents of 10 members of the second and third generations in our family who lived in Alabama, nor do we know whether they were victims of the disease. The cases reported by Corson and Perlman,[6] Frank,[7] Franks and Davis,[8] Franks, Davis, and Dobes,[9] Robinson,[10] and Lamb and Halpert [11] are not included in our chart (i. e., initials do not agree with any of ours), but it is possible that some other families previously reported are included.

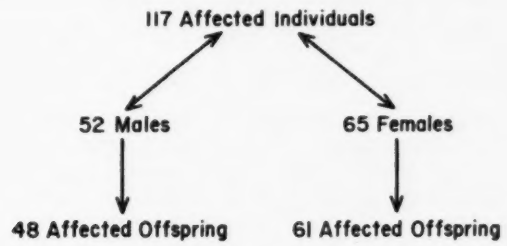


Fig. 6.—Diagram indicating that men and women alike transmit the factor approximately equally to male and female offspring.

Test [12] suggested that all but one family, possibly two, in which epidermolysis bullosa had been reported prior to 1945 and in which the condition had been transmitted through several generations, belonged to the large family reported by Johnson and Test. These would not have included, then, the small group in northern

4. Greenberg, S. I.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **49**:333-334 (May) 1944.

5. Thompson, R. G.; Leedham, C. L., and Hailey, H.: Epidermolysis Bullosa Hereditaria, South. M. J. **42**:647-653 (Aug.) 1949.

6. Corson, E. F., and Perlman, H. H.: Epidermolysis Bullosa Hereditaria, M. J. & Rec. **136**:67-68 (July 20) 1932.

7. Frank, S. B.: An Unusual Variant of Epidermolysis Bullosa, Arch. Dermat. & Syph. **47**:327-334 (March) 1943.

8. Franks, A. G., and Davis, M. I. J.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **47**:647-650 (May) 1943.

9. Franks, A. G.; Davis, M. I. J., and Dobes, W. L.: Epidermolysis Bullosa, Urol. & Cutan. Rev. **49**:57-65 (Jan.) 1945.

10. Robinson, M. M.: Epidermolysis Bullosa Hereditaria, Urol. & Cutan. Rev. **50**:545-561 (Sept.) 1946.

11. Lamb, J. H., and Halpert, B.: Epidermolysis Bullosa of the Newborn, Arch. Dermat. & Syph. **55**:369-374 (March) 1947.

12. Test, A. R.: Personal communication to the authors.

Alabama studied by Thompson, Leedham, and Hailey in 1948 and 1949, nor possibly the family, also from Alabama, reported in 1942 by Leider and Baer.[13] Several members of our family were hospitalized while in the armed services during World War II and were discharged because of epidermolysis bullosa. At least one of them thought that some members of his immediate family had been reported in the medical literature as having had the same disease.

Cartledge and Myer stated that the first person in this country reported to have epidermolysis bullosa, and included in their family, was an Irish immigrant of about 1770 who settled in what is now West Virginia. Test pointed out that the afflicted progenitor of that family was actually the wife of this Irish immigrant and was Welsh rather than Irish. If the family reported by Cartledge and Meyer is connected with the one reported here, the connection was prior to their immigration to the western hemisphere.

Information gained from various members of the presently reported family suggests that the factor responsible for the disease was transmitted from a family of English extraction which migrated to South Carolina from New England about 1760. The fact that Cockayne,[14] Haldane and Poole,[15] and others have reported the presence of epidermolysis bullosa in England is compatible with the belief that one of these families of English extraction may have introduced the disease into this country.

SUMMARY AND CONCLUSIONS

A genealogic chart of a family of 283 persons in which epidermolysis bullosa simplex was inherited through eight generations is reported. Fifty-two males and sixty-five females were known to have had the disease. Two hundred and eighty descendents of normal siblings of epidermolysis victims are reported but not included in the chart.

In Alabama the incidence of this form of the disease is not rare.

Although bullae occurred more commonly on the hands and feet, members of this family frequently exhibited bullae on other areas of their body when subjected to trauma.

The ratio of normal to affected persons did not deviate significantly from a 1 to 1 ratio. There occurred also no significant deviation from a 1:1 ratio of males to females, either exhibiting the disease or transmitting the factor. At least one parent had to have bullae, if the factor on which they were dependent was transmitted to the offspring. Thus, these findings support the simple-dominant hypothesis of inheritance of the factor.

It appears that consanguinity is insignificant in the transmission of this type of epidermolysis bullosa.

The first reported marriage of two victims of epidermolysis bullosa simplex is here included. The fact that their single offspring was normal offers final evidence for the dominant-factor hypothesis.

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13. Leider, M., and Baer, R. L.: Epidermolysis Bullosa Hereditaria, Arch. Dermat. & Syph. **46**:419-424 (Sept.) 1942.

14. Cockayne, E. A.: Recurrent Bullous Eruption of the Feet, Brit. J. Dermat. **50**:358-362 (July) 1938.

15. Haldane, J. B. S., and Poole, R.: A New Pedigree of Recurrent Bullous Eruption of the Feet, J. Hered. **33**:17-18 (Jan.) 1942.

Evidence was obtained that the factor responsible for epidermolysis bullosa simplex was, in the family reported herein, introduced into America through an English immigrant family which came to New England and migrated from there to the South. This introduction into America is known to be independent of most families heretofore reported.

620 S. 20th St. (3) (Dr. Noojin).

Mary Virginia Stallworth rendered valuable assistance in this study.

ABSTRACT OF DISCUSSION

Dr. Howard Hailey, Atlanta: Epidermolysis bullosa hereditaria is an uncommon skin disease. I have observed and cared for affected persons from two unrelated (so far as known) family groups. Among the interesting features of this condition is the comparative lack of disability in some affected persons.

One of my patients, a man aged 40, of Irish descent, reported that after digging post holes for a fence the bullae in the palms and on the palmar surface of the fingers were enormous. However, he did not discontinue his regular occupation as an auto mechanic. No doubt, this is possible because of the relative superficial character of the bullae in the simplex type.

[Dr. Hailey presented a genealogic chart representing one of the families previously reported. Eleven males and six females were known to be affected in five generations.]

Dr. Noojin deserves thanks for a thorough genetic study of the simplex type of epidermolysis bullosa hereditaria.

Dr. Reuben Nomland, Iowa City: How do you explain the sporadic cases without a history of familial disease?

Dr. Ray O. Noojin, Birmingham, Ala.: I wish to thank Dr. Hailey for his kind remarks. In the table a classification of the various types of epidermolysis bullosa was shown. It is known that isolated cases of both major forms of the condition have been reported in which there was no history of this dermatosis having occurred previously in any member of the family. In these cases it is impossible to be absolutely certain that the histories are unquestionably valid. Nevertheless, a number of them are reported as having been encountered.

Clinical Notes; New Instruments, and Techniques

AN EFFECTIVE ANTIPRURITIC TAR APPLICATION

THOMAS S. SAUNDERS, M.D.
PORTLAND, ORE.

In prescribing local applications for the relief of anogenital pruritus, I have not been impressed by their efficiency. I have constantly sought some local measure which would afford prompt relief while the patient's condition was being evaluated.

Recently a colleague (Will C. Davis, M.D.†) developed a formula which was found quite satisfactory. The prescription is as follows: solution coal tar, 6 cc.; tincture of benzoin, plain, 12 cc., and acetone to make 60 cc.

Because of its irritating properties its use is limited to noninflamed, nonexcoriated areas.

Of 14 consecutive patients with anogenital itching, 12 obtained prompt and satisfactory relief following local application of the medicament from the above formula. One patient failed to experience any relief, and one was unable to use the treatment because of local irritation.

We have found that in many cases when anogenital itching is capable of being relieved, the annoying sensation ultimately disappears.

Because of the carcinogenic properties of tar, the prescription is nonrefillable, in order to discourage its protracted use.

1020 S. W. Taylor St.

†Dr. Davis died on June 23, 1951.

PARENTERAL MULTIVITAMIN THERAPY OF RECALCITRANT ACNE VULGARIS

HENRY M. LEWIS, M.D.
EGBERT J. HENSCHEL, M.D.
and
GERALD M. FRUMESS, M.D.
DENVER

In November, 1950, Kline [1] reported an excellent clinical response in patients with therapy-resistant acne vulgaris following the parenteral administration of an aqueous multivitamin solution. Stimulated by his enthusiasm, we endeavored to corroborate his results.

The preparation employed was the same as that used by Kline in his study. Each 2 cc. of this preparation contains 10,000 U.S.P. units of vitamin A, 1,000 U.S.P. units of calciferol (vitamin D_3), 10 mg. of thiamin hydrochloride, 1 mg. of riboflavin, 3 mg. of pyridoxine hydrochloride, 20 mg. of nicotinamide, 50 mg. of ascorbic acid, and 2 mg. of alpha-tocopherol, in an aqueous solution containing 4% weight per volume of sorbitan monolaurate derivative with 0.5% chlorbutanol as a preservative.[2]

1. Kline, P. R.: Role of Parenteral Multivitamin Therapy in the Treatment of Acne, Arch. Dermat. & Syph. **62**:661 (Nov.) 1950.

2. Dr. Louis Freedman of the U. S. Vitamin Corporation supplied the preparation (visyneral® injectable) used in this study.

No attempt was made to employ this preparation for average acne patients. Only those patients who had not responded satisfactorily to ordinary therapeutic measures, including x-ray therapy, were included in this study. As a result, our evaluation may not be indicative of therapeutic effectiveness in general practice.

We felt that adequate clinical evaluation could be achieved in 20 patients. This therapy was started for a number of others, but lack of prompt response necessitating alternative measures, and/or irregular observation vitiated adequate experimental data in their cases. The study was carried on over a period of six months.

There were 17 females and 3 males; the age range was 14 to 24. Two cubic centimeters of the multivitamin preparation was administered intramuscularly at weekly intervals; the number of injections varied from a minimum of 5 to a maximum of 20; the average was 8.3 injections per patient. Although ultraviolet radiation by cold quartz-mercury vapor lamp was used concomitantly in many instances, the previous beneficial effects from its use were already evaluated, and we were in a position to note whatever additional benefit might be attributable to the multivitamin injections.

In no case were we able to observe a "cure." However, only 3 of the 20 patients failed to note at least subjective improvement. Definite objective improvement was noticed in six patients and moderate objective improvement in four patients.

Definite value	6
Moderate value	4
Questionable value	7
No value	3
Total treated	20

Persons with recalcitrant acne vulgaris will at times display spontaneous improvement due to unassessable alterations in their dietary, nervous, or endocrine status. As a result, a truly scientific evaluation of any auxiliary therapeutic measure is difficult to achieve, for rigid experimental controls are lacking. Despite this consideration, however, our results indicate that under the conditions of this study, the multivitamin preparation employed is a helpful adjuvant measure in some cases of obstinate acne vulgaris.

2200 E. 18th Ave. (6)

FIXED DRUG ERUPTION DUE BOTH TO AUREOMYCIN AND TO TERRAMYCIN

Report of a Case

JOHN W. DOUGHERTY, M.D.
NEW YORK

Nineteen totally unrelated drugs have been reported as instigators of that peculiar form of localized hypersensitivity known as "fixed drug eruption."[1] The following is the case history of a hitherto unreported sensitization which appeared after the ingestion of both aureomycin and terramycin.

REPORT OF CASE

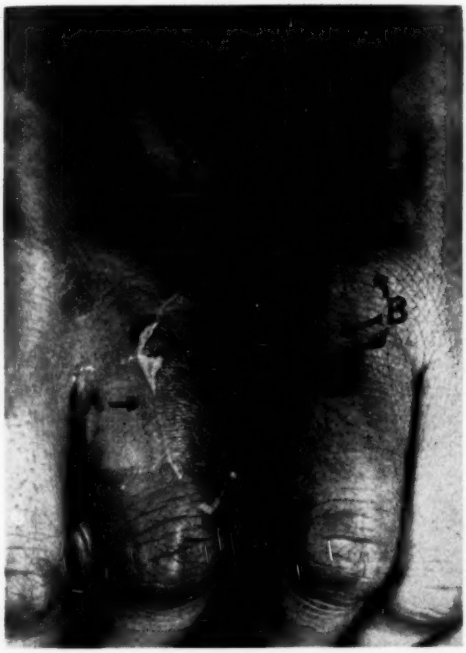
I. S., a 29-year-old physican, was first treated with aureomycin, 0.5 gm. four times daily, in May, 1950, for a generalized furunculosis due to Staphylococcus aureus. No untoward reaction was noted during the five days of therapy. This course was repeated in July, 1950, again with no harmful side results.

From the Department of Medicine (Dermatology), New York Hospital and Cornell University Medical College.

1. Abramowitz, E. W., and Noun, M. H.: Fixed Drug Eruptions, Arch. Dermat. & Syph. **35**:875 (May) 1937.

In September, 1950, one-half hour following the ingestion of 0.5 gm. of aureomycin, violaceous, urticarial, pruritic plaques, varying in diameter from 1 to 5 cm., appeared on the dorsal surfaces of the hands, feet, and penis. The medication was continued, and the eruption disappeared after 48 hours, leaving hyperpigmented macules as sequelae. Coincidentally, a mild, long-standing dermatophytosis (positive for fungi on a slide preparation) flared. This was controlled by local application of a fungicidal ointment and has not recurred.

In November, 1950, one-half hour after he took aureomycin, urticarial lesions appeared in the sites marked by the residual hyperpigmented macules mentioned previously. The drug was discontinued, and the urticarial component disappeared, leaving the excess pigment deposition as before. Ten days later, terramycin therapy in the same dosage was instituted, with a recurrence of the urticarial element in exactly the same sites.



A, site of a healing furuncle; *B*, several hyperpigmented macules representing fixed drug eruption.

Some scaling over the surfaces of the wheals was noted, and, because of the history of the flare of the dermatophytosis during the first attack, cultures and slide preparations of the lesions were made. These showed the lesions to be negative for fungi.

No treatment reaction was noted to penicillin, tyrothricin, or sulfonamides, and when taken during the ensuing weeks these drugs did not incite whealing in the hyperpigmented macules.

SUMMARY

Aureomycin and terramycin, two drugs of markedly similar spectrum of antibiotic activity, are reported as the causes of a fixed drug eruption in the same patient.

66 E. 66th St. (21)

WEBER-CHRISTIAN DISEASE OCCURRING IN A NEGRO WOMAN

M. H. SAMITZ, M.D.
AND
J. M. COLETTI, M.D.
PHILADELPHIA

The purpose of this paper is to report another case of Weber-Christian disease and to present what we believe to be the second case reported in a Negro.[1] In addition, the unusual feature previously reported [2] of progressive necrosis of the pannicula adiposa leading to spontaneous rupture and drainage of the subcutaneous nodules was also observed.

Weber-Christian disease is of unknown origin, and it is not the purpose of this report to discuss the controversial theories as to its cause.[3] However, the sudden and often explosive character of the appearance of these nodules makes one postulate an allergic mechanism.

Pfeiffer first described this condition in 1892, and Weber [3e] later reported a case in which he labeled the condition relapsing nonsuppurative nodular panniculitis. In 1928 Christian,[4] in his report of the third case, suggested adding "febrile" to Weber's definition. Since then it has been referred to as relapsing febrile nodular nonsuppurative panniculitis, and for the sake of brevity it is termed Weber-Christian disease. Approximately 48 cases of this comparatively rare disease have been reported. The syndrome has been reported in white persons and Orientals, but only one instance of its occurrence in Negroes has been reported in the literature.

The condition is seen predominantly in the second to fourth decades, although cases have been recorded occurring in the age range of six months to 70 years. Obesity and sex apparently are important factors, for the disease appears most commonly in obese women. In approximately 75% of the cases reported the patients were women.

Weber-Christian disease is characterized by generalized malaise and recurrent bouts of fever, usually followed by the appearance of subcutaneous nodules having a tendency to heal with a depression of the skin. These nodules are ushered in by malaise and fever and may vary in size from 1 to 20 cm.[4a] They occur on the trunk and extremities but predominantly on the thighs. They are less common on the breast. These nodules are freely movable and of firm consistency, The majority are tender to touch, and many are painful from the time of appearance to the state of involution. The color of the nodules varies from that of normal skin to violaceous. Many heal with no noticeable skin sequelae, and others heal with depression of the epidermis at the site of the nonsuppurative focus. Depression is the result of fibrosis at the site of fat atrophy,

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From the Department of Dermatology and Syphilology (Service of Dr. M. H. Samitz), Graduate Hospital of the University of Pennsylvania.

1. Johnson, W. A., and Plice, S. G.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Arch. Path. **48**:281-286 (Oct.) 1949.

2. (*a*) Binkley, J. S.: Relapsing Febrile Nodular Nonsuppurative Panniculitis: Report of a Case, J. A. M. A. **113**:113-116 (July 8) 1939. (*b*) Freidman, N. B.: Fatal Panniculitis, Arch. Path. **39**:42-46 (Jan.) 1945. (*c*) Miller, J. L., and Kritzler, R. A.: Nodular Nonsuppurative Panniculitis, Arch. Dermat. & Syph. **47**:82-96 (Jan.) 1943. (*d*) Shaffer, B.: Liquefying Nodular Panniculitis: Report of a Case, Arch. Dermat. & Syph. **38**:535-544 (Oct.) 1938.

3. (*a*) Alderson, H. E., and Way, S. C.: Relapsing Febrile Nonsuppurative Panniculitis (Weber), Arch. Dermat. & Syph. **27**:440-449 (March) 1933. (*b*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Chritsian Disease), J. A. M. A. **109**:1419-1425 (Oct. 30) 1937. (*c*) Miller and Kritzler.[2c] (*d*) Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1934, Vol. 4, Pt. 4, p. 804 (55-58). (*e*) Weber, F. P.: Case of Relapsing Nonsuppurative Nodular Panniculitis Showing Phagocytosis of Subcutaneous Fat Cells by Macrophages, Brit. J. Dermat. **37**:301-311, 1925; (*f*) A Further Note on Relapsing Febrile Nodular Nonsuppurative Panniculitis, ibid. **47**:230-235, 1935.

4. Christian, H. A.: Relapsing Febrile Nodular Nonsuppurative Panniculitis, Tr. A. Am. Physicians **43**:266-271, 1928.

4a. Reed, A. C., and Anderson, H. H.: Relapsing Nonsuppurative Panniculitis, California & West. Med. **47**:325-327, 1937.

which is the usual termination of these masses, but should the inflammatory reaction be severe enough to produce necrosis with liquefaction, spontaneous rupture may result. The drainage has been reported as mucoid, yellow or greenish, or semipurulent. Demonstration of bacteria or growth on cultures from a lesion has been reported, but it has not been established whether the organism was a primary or secondary invader. Fever, usually a part of this disease, may be absent. Frequently it is recurrent in nature, and temperature has been recorded as high as 104 F.[5] Relapses are common and may occur at any time without any regular time sequence.

The characteristic histological features have been described by Bailey,[3b] and the integration of the history, clinical picture, and histopathologic findings suffices to establish the diagnosis. Since the disease is relapsing in nature, recovery to the degree of being complete is not always certain. Spontaneous cures have been claimed; however, fatalities have also been reported.[6]

Treatment has been mainly symptomatic. A host of "cures" have been reported, but these could well have been spontaneous remissions, since duplication of results has not been very fruitful. If this condition is allergic in origin, the administration of the adrenocorticotropic hormone may be beneficial. It is our intention to follow this course of therapy when the patient experiences another relapse.

REPORT OF A CASE

M. P., a 21-year-old Negro woman, was admitted to the dermatologic service of the Graduate Hospital of the University of Pennsylvania with the complaint of "painful bumps" on the legs, thighs, arms, trunk, and breasts. She stated that she was in good health until July, 1948, at which time four or five nodules appeared on the thighs and legs. One of the nodules later became very tender, ruptured spontaneously, and drained a substance which was described as a "yellow fluid." The remainder of the nodules disappeared in about two weeks. The patient was not certain whether she had fever but often felt hot and chilly. She remained well for six months and then noted the reappearance of "many of these bumps" which were distributed over the arms, back, breast, abdomen, thighs, and legs. Several lesions were tender. Three or four ruptured spontaneously and again drained a "yellow fluid." She described these nodules as red and purple and varying in size from that of a small pea to that of an egg. Her physician administered penicillin and streptomycin by injection and aureomycin orally with no benefit. This sequence of events persisted up to the time of her hospital admission. The interval between appearance of these nodules was about three to six months, and they would remain about two weeks. She denied ingestion of bromides or iodides, but at the onset of the disease took acetylsalicylic acid or anacin® (acetphenetidin, acetylsalicylic acid, quinine sulfate, and caffeine alkaloid) when the nodules were painful. For the past two months she denied taking any form of medication.

The family history was noncontributory. The patient has a twin sister (identical) who is well.

The past medical history revealed that she had had measles, mumps, and whooping cough as a child with no sequelae. An appendectomy was done five years ago, and recovery was uncomplicated. Menstruation was regular.

Physical examination showed a well-nourished, slender, 21-year-old Negro woman. She was cooperative and intelligent. Evaluation of all systems and organs other than the skin and subcutaneous tissue was within normal limits.

On the breast regions there were several hyperpigmented depressed scars and two tender subcutaneous nodules. Three tender subcutaneous nodules were present on the back, and seven tender erythematous and violaceous nodules of varying sizes and several depressed hyperpigmented scars were present on the buttocks. Similar scars were present on both thighs and legs. Twelve subcutaneous nodules, varying from pink to bluish-red, of which only a few were tender, were also

5. (*a*) Jones, P. E.; Lamb, J. H., and Goldman, L.: Panniculitis, South. M. J. **43**:792-799, 1950. (*b*) Spain, D. M., and Foley, J. M.: Report on Weber-Christian Disease, Am. J. Path. **20**:783-787, 1944.

6. Freidman.[2b] Jones, Lamb, and Goldman.[5a] Miller and Kritzler.[2c] Mostofi, F. K., and Engleman, E.: Fatal Relapsing Febrile Nonsuppurative Panniculitis, Arch. Path. **43**:417-426 (April) 1947.

present on both lower extremities. Two of the thigh nodules were draining lesions which had ruptured spontaneously about five days prior to hospital admission. The drainage material which was described as a "yellow fluid" initially was now purulent in character.

Laboratory studies showed the urine to be normal and the blood count to be as follows: hemoglobin, 69% or 11.5 gm.; red cells, 4,080,000; white cells, 5,800; neutrophiles, 68%; lymphocytes, 28%; eosinophiles, 1%; monocytes, 2%, and basophiles, 1%. Repeated white cell counts never exceeded 6,800. The total serum protein was 7.96 mg. per 100 cc. (albumin 4.66 and globulin 2.30). The basal metabolism rate was +2. Results of multiple agglutination tests were negative for Salmonella (Eberthella) typhosa "O" and "H," Brucella, and Proteus OX19. The blood sugar was 87 mg. per 100 cc. A direct van den Bergh test of serum elicited a negative reaction, and an indirect test less than 0.2%. Erythrocyte fragility was within normal limits. Serologic reaction for syphilis was negative. The sedimentation rate was 37 mm. in 60 minutes (Westergren). There was no sickling. The results of roentgenologic examination of the chest and legs were normal. An electrocardiogram was reported as normal. The reaction to tuberculin test (purified protein derivative, first strength) was 4+.

Cultures from a ruptured focus showed Staphylococcus aureus, whereas material aspirated from a fluctuant nodule from the pretibial region elicited no bacterial growth. Guinea pig inoculation of this aspirated material was also sterile.

Nodules from the left thigh and right leg were excised for histologic study and were reported upon as follows:

The section of skin showed relatively normal epidermis and corium, the corium being somewhat on the thin side. Pathologic changes began about at the level of the sweat glands and consisted of an infiltrate involving the fat that appeared to be composed of reticulum cells, macrophages, lymphocytes, and varying number of eosinophiles. This reaction, as one proceeded downward in the section, changed to an area containing more polymorphonuclear leucocytes and some necrosis. One saw a large cavity within the section that probably was filled with necrotic debris. As one proceeded downward still farther in the section, the reaction to the fat became less pronounced. Here and there one saw tracks of fibrosis running through the section. Numerous dilated capillaries were seen. The blood vessels observed throughout the section appeared to be normal. This did not appear to be a disease of the vascular tree but rather one of the fat. No tuberculoid structures or giant cells were seen. Large foam cells were visualized throughout the fat.

The pathological diagnosis, reported by Dr. H. Beerman, was nonsuppurative panniculitis.

After two weeks hospitalization the nodules disappeared spontaneously. The two draining lesions healed with scarring. Temperature varied from 98.2 to 103 F. for 10 days and then became normal. The patient was discharged at the end of three weeks to the outpatient department for follow-up study. A new crop of lesions occurred two months later. A three-week trial of sulfapyridine, as suggested by Arnold,[7] had no appreciable beneficial effect. With supportive measures, spontaneous involution occurred.

SUMMARY

A case of relapsing febrile nodular nonsuppurative panniculitis is presented.

It is unusual in that, so far as we can ascertain, this represents the second case reported in a Negro.

The necrosis in many of the nodules progressed to liquefaction and terminated in spontaneous rupture with drainage.

Bacteriologic studies of aspirated material failed to demonstrate bacteria.

Penicillin, streptomycin, and sulfapyridine did not alter the course of the disease.

1715 Pine St. (3)

7. Arnold, H. L., Jr.: Nodular Nonsuppurative Panniculitis (Weber-Christian): Preliminary Report of a Case Controlled by Sulfapyridine, Arch. Dermat. & Syph. **51**:94-99 (Feb.) 1945.

PODOPHYLLIN TREATMENT FOR PLANTAR WARTS

LIEUTENANT DONALD V. WALZ
MEDICAL CORPS, UNITED STATES AIR FORCE

It is the purpose of this report to describe the successful use of podophyllin in treatment of 13 patients with verruca plantaris, of whom 11 were cured. The patients remained ambulatory during the treatment, and no discomfort was encountered. There has been no recurrence after four to six months' observation of the 11 cured patients.

In 1948, Kurtin and Yantef[1] first reported the successful use of podophyllin in the treatment of plantar warts. Their method consisted of paring down the wart until bleeding points were encountered. The surrounding area was coated with collodion, and a drop of a 25% solution of podophyllin in liquid petrolatum was then placed into the concavity. A 2-in. (5-cm.) strip of well-flamed tape was placed over the lesion to macerate the area. This treatment was repeated at eight-day intervals, usually for three to four treatments. These authors reported 60% cures in a small series of cases.

The technique I have employed is as follows: The wart is pared down until the red capillary ends are seen. A 25% solution of podophyllin in benzoin tincture is applied with an applicator to the area and left to dry for 20 to 30 minutes. A petrolatum dressing is then applied over the area. The patient removes the bandage and bathes as usual that night. This treatment is repeated at five- to seven-day intervals. After two treatments a marked change in the wart usually becomes evident. There is marked relief from pain, and the piling up of keratin slows down remarkably. The lesion gradually becomes smaller in diameter as well as in thickness, being replaced by normal-appearing skin. After 8 to 10 treatments, the area is usually completely free of all evidence of the wart. The patient complains of little or no discomfort, and no crater or raw areas are present.

This method of repeated paring down of the wart and application of podophyllin was tried for 13 patients with plantar warts, with apparent cures, from four to six months without recurrence, in 11 of these and improvement in 2. The treatments necessary for cures varied from 1, for two patients, to 10, for one patient. In all patients who were apparently cured, the wart area was replaced gradually by normal-appearing skin. One patient in particular had a very large mosaic wart, approximately 1¼ in. (34 cm.) in diameter and elevated ⅜ to ½ in. (0.95 to 1.27 cm.), that had resisted repeated and various attempts at cure. The wart disappeared completely in eight treatments, without recurrence in six months.

Podophyllin is a powder, clear light brown to greenish yellow. It is an irritant and an active purgative, which is the basis for its inclusion in many proprietary "liver pills" Podophyllin seems to act directly on epithelial cells, producing degeneration and bizarre cell forms interpreted as distorted mitotic figures.[2]

The method described here requires continuous and repetitious treatment to obtain a cure. However, it is free of discomfort for the patient and does not prevent him from pursuing his usual occupation. Because of the ease of application, this method is especially advantageous when x-ray therapy is not readily available.

Rapid City Air Force Base, Weaver, S. D.

1. Kurtin, A., and Yantef, R.: Podophyllin Therapy for Plantar Warts, Arch. Dermat. & Syph. **57**:395-396 (March) 1948.

2. King, L. S., and Sullivan, M.: Effects of Podophyllin and of Colchicine on Normal Skin, on Condyloma Acuminatum and on Verruca Vulgaris: Pathologic Observations, Arch. Path. **43**:374-386 (April) 1947.

Society Transactions

ATLANTIC DERMATOLOGICAL CONFERENCE

March 3, 1951

Paul E. Bechet, M.D., and Isadore Rosen, M.D., *Co-Presidents*

Anthony C. Cipollaro, M.D., and George M. Lewis, M.D., *Co-Secretaries*

Rosacea-like Tuberculid. Presented by DR. WILBERT SACHS, New York.

R. R., a woman aged 31, was first examined in the dermatology clinic of New York Hospital on Dec. 1, 1950, because of an eruption of four months' duration on the face. This began along the mandibular margins and spread upward to involve the cheeks.

There is a diffuse erythematous maculopapular eruption of the lateral thirds of the face, rather sharply demarcated at its borders about the eyes and along the mandibular margin. Some telangiectasia is present. Diascopic pressure reveals typical "apple-jelly" nodules.

Serologic tests for syphilis gave negative reactions. A roentgenogram of the chest was normal, and the reaction to the tuberculin test was strongly positive in a dilution of 1 : 1,000,000.

Biopsy of the midcutis and upper cutis showed numerous tubercles composed of small round cells, wandering connective tissue cells, and epithelioid cells. There was an occasional giant cell. The reaction was focused mainly about the hair follicles. The blood vessels were dilated, and there was a moderate perivascular infiltrate. The epidermis was flattened and otherwise unchanged. The histologic diagnosis was rosacea-like tuberculid of Lewandowsky and Lutz.

The patient has been treated with white lotion (lotio alba) and weekly mild erythema doses of ultraviolet light. There has been some improvement.

Rosacea-like Tuberculid. Presented by DR. FRANK E. CORMIA, New York.

DISCUSSION ON TWO PRECEDING CASES

DR. MAURICE J. COSTELLO, New York: The only success I have had in treating these patients was with increasing doses of tuberculin.

DR. FRANCIS P. MCCARTHY, Boston: My impression is that this disease is much commoner than we are led to believe. If biopsies were performed more frequently in cases of rosacea, although it is not practical to do so because of the location of the eruption, I think we would find the incidence somewhat higher. I am under the impression that I have treated lesions similar to this in the routine way and that they have cleared.

DR. FRANK E. CORMIA, New York: My colleagues and I considered the lesion in both of these cases rather typical of rosacea-like tuberculid. Clinically, at least, they fitted that description fairly well, although a considerable element of seborrhea and some of the clinical features of rosacea are present. However, biopsy showed the type of infiltration that one would expect in a true tuberculid. I should like to call attention to the fact that the reaction to tuberculin was strongly positive in great dilution in these cases.

DR. HARRY BELLACH, New Britain, Conn.: In both of these cases I suggest the use of dihydrostreptomycin, *p*-aminosalicylic acid, or amithiozone (tibione®), either alone or in combination. Viomycin was recently found to be effective in suppressing tuberculosis in guinea pigs (Karlson, A. G., and Gainer, J. H.: *Proc. Staff Meet., Mayo Clin.* **26**:53 [Jan. 31] 1951). The use of this drug is worthy of consideration also.

† Dr. Hopkins died on Feb. 27, 1951.

DR. FRANK EICHENLAUB, Washington, D. C.: I was just about to question whether most of the cases presented as tuberculid are not really rosacea. The microscopic picture is hardly conclusive proof.

DR. ROBERT STOLAR, Washington, D. C.: Recently, I was discussing a case of this type with one of the officers of the tuberculosis service at Walter Reed Hospital, Washington, D. C., who had had excellent success by treatment with old tuberculin and streptomycin. The tuberculin in some way created a greater susceptibility to treatment with streptomycin.

DR. W. F. LEVER, Boston: I, too, believe that many of the lesions that we call rosacea-like tuberculid on histologic grounds are nothing but rosacea. I have repeatedly seen tuberculoid formations in biopsy specimens obtained from patients with typical rosacea.

DR. DAVID BLOOM, New York: I have used successfully the treatment for rosacea in several cases in which the condition was diagnosed by the pathologist as rosacea-like tuberculid. This makes me doubt that the pathologist can always distinguish a case of simple rosacea from one of Lewandowsky's tuberculid.

Macular Atrophy (Schweninger-Buzzi Type). Presented by DR. PAUL GROSS, New York.

A. S., a woman aged *32*, complains of an eruption of the face and shoulders of 10 years' duration. This began as an attack of hives which subsided within three months following elimination of certain foods. When she was first seen in 1945, there were four lesions on the face and five in the midcapsular region. Since then, the lesions on the trunk have steadily increased in number, but there has been no change in the lesions on the face.

On the right side of the nose are two circumscribed purplish-red maculas, slightly raised and covered by glistening skin with a few telangiectases. There is a similar lesion over the right eyebrow. On the left side of the nose is a dime-sized lesion typical of anetoderma. The shoulders are covered with many plaques, somewhat raised, mostly skin-colored, and soft in consistency. They are of varying size, the largest being about that of a half-dollar. The skin on the surface of the tumors is wrinkled, and many of the raised plaques can be pressed down in a hernia-like fashion. Some of the small lesions have a purplish tint, indicating inflammatory reaction, and others are skin-colored and consist only of macular atrophy.

Results of biopsies on the face and back were consistent with macular atrophy, the section from the face showing more inflammatory changes than that from the back.

DISCUSSION

DR. FRANCIS A. ELLIS, Baltimore: We have seen a fair number of cases of macular atrophy in Negroes. The unusual features in this case are the type of lesions on the face and the infiltration in some of the lesions on the body. Infiltrated lesions are usually seen in Negroes, owing to the fact that they have a keloidal tendency and usually have some fibrosis. This could account for the induration in several of the lesions. Usually the fibrosis cannot be demonstrated because the biopsy was not performed from an infiltrated plaque.

DR. ROBERT STOLAR, Washington, D. C.: A patient was recently presented before the Baltimore-Washington Dermatological Society with a fairly classic anetoderma and a positive reaction for albumin in the urine. As it was thought that the condition might be collagen vascular disease, the patient was given corticotropin (ACTH), in a total of about 600 mg., and the albumin precipitated much more than before. After the corticotropin therapy was discontinued, the lesions receded somewhat, the doughy feel became much less prominent, and the lesions couldn't be pushed in as they could prior to treatment. This condition may be related to the collagen vascular syndrome, if this case is an example of what corticotropin does for it.

DR. PAUL GROSS, New York: This case demonstrates that even primary macular atrophy is preceded by inflammatory changes. The history of urticaria preceding macular atrophy can be found in other cases reported in the literature. A classic case of this type is the one reported by Pellizzari as *"eritema orticato atrofizante."*

Keratosis Follicularis. Presented by DR. FRANK E. CORMIA, New York.

D. S., a girl aged 17, has an eruption of the scalp, face, neck, shoulders, and hands, of nine and a half years' duration. The family history is irrelevant. The patient was subject to hives from the age of 11 to 12 and had another transient attack three years ago. She had been treated for mild anemia in the past six months.

Nine years ago the scalp became dry and scaly; eight years ago discrete crusted lesions were noted in the scalp. After another year, the lesions became confluent and were noted on the sides and back of the neck. The shoulders became involved five years ago, the forehead and hands, three years ago, and the circumoral region, three months ago. The eruption is ordinarily at its height, with severe itching, during the summer months, with great to complete involution during the winter. She has been bothered continuously, however, for the past year and a half.

Residual crusted lesions in the scalp and mild dermatitic lesions on the forehead are present. A severer crusted dermatosis can be seen on the lateral aspects of the neck and the adjacent portions of the shoulders. Nonspecific dystrophic lesions are present on the fingernails and small papular lesions on the hands.

Biopsy was performed in another city, and the findings were said to be compatible with familial benign chronic pemphigus or keratosis follicularis.

Through the years various types of therapy have been given, with emphasis on large doses of iron preparations, vitamin A, and other vitamins. Benefit has been minimal. When I first saw the patient, she was receiving an iron preparation for secondary anemia and aureomycin, 1 gm. daily. The dose of the latter was increased to 2 gm. daily and its administration continued for three weeks, and aureomycin ointment was prescribed. Because of lack of improvement, aureomycin administration was stopped, and combined therapy with liver extract given intramuscularly, vitamin B_{12}, carbarsone, 0.5 gm., and 20% colloidal sulfur ointment was instituted, with about 30% improvement in a month. Two injections of cortisone, 100 mg., were given on alternate days, but considerable progression was noted after the second injection. She was given sulfadiazine, 60 grains (3.9 gm.) daily, in two courses of four weeks each, with improvement on only the first course. Large doses of vitamin D_2 were ineffectual. A single fractional dose of x-rays caused a severe exacerbation. Recently, an iron preparation, a liver preparation, vitamin B complex, and conjugated estrogenic substances (premarin®) have been prescribed.

DISCUSSION

DR. FRANCIS A. ELLIS, Baltimore: The fact that the eruption started when the patient was very young certainly makes the prognosis worse. As time goes on, I think she will have lesions in other areas. She says there are none about the vagina, anal region, etc., but one would expect them to occur there. I am a little surprised that aureomycin treatment didn't help, although I think any result of therapy is more or less temporary. Improvement in winter, which occurs in Hailey-Hailey disease (chronic benign familial pemphigus), certainly isn't seen in any form of pemphigus that I know. The verrucous lesions on the dorsa of the hands are typical of the nonvesicular (dryer) form or keratosis follicularis (Darier's disease).

DR. MARK HOLLANDER, Baltimore: There is always a large question about therapy in this disease. In one of the cases to which Dr. J. L. Fromer referred, a case presented by Dr. Herman Beerman, of Philadelphia, it was suggested that grenz rays be used. I do not know whether that suggestion was followed or what the results may have been. I was surprised to see that an exacerbation occurred in the present patient after a fractional dose of x-rays. This disease, being an epidermal lesion, ordinarily responds quite well to grenz rays, and I suggest that this therapy be tried for the girl's benefit.

DR. MAURICE J. COSTELLO, New York: My impression is that all forms of light therapy are contraindicated in keratosis follicularis. I have found that one of the things that always makes the condition of these patients worse is exposure to sunlight. I think that use of grenz rays is contraindicated for that reason.

DR. E. E. BARKSDALE, Washington, D. C.: I agree with Dr. Costello. I think any type of radiation in this kind of case is contraindicated. The patient has photosensitivity and a nickel dermographia. If you get rid of her costume jewelry her condition might improve.

DR. HARVEY BLANK, Philadelphia: I can speak of only one case of keratosis follicularis; the patient was treated with grenz rays through ports approximately 2 in. (5 cm.) square. The patient had extensive lesions on the trunk, which made him an excellent subject for trial of the therapy. We found it necessary to use 1,000 r at 15 kv. With 1,000 r an acute inflammatory reaction was produced in the lesions for two or three weeks, which then subsided leaving normal skin. Very few lesions of keratosis follicularis have recurred in these areas during 14 months' follow-up observation. The man happened to have a fairly hairy chest, but there was no loss of hair during the acute inflammatory reaction or subsequently. I haven't treated lesions on the face or other areas exposed to light, but the treatment should not be condemned categorically.

DR. HARRY M. ROBINSON JR., Baltimore: I published a report (ARCH. DERMAT. & SYPH. **62**:137 [July] 1950) concerning a woman in whom the eruption was limited to the right lower extremity and developed several months after a severe sunburn. X-ray therapy was given in divided doses of 50 r each, to a total of about 600 r, with no response. Large doses of vitamin A given over a period of six months also did not help.

DR. PAUL GROSS, New York: The effect of sunlight on this disease should be interpreted as Koebner's phenomenon brought about by a physical agent. It is not surprising that this occurs in the dermatosis which is related to vitamin A deficiency. I have observed the same phenomenon in pityriasis rubra pilaris, and I believe it can readily be compared with the lesions of pellagra which are produced by sunlight.

DR. FRANK EICHENLAUB, Washington, D. C.: About 20 years ago I presented a case of keratosis follicularis before this organization. The patient had been given fractional x-ray therapy with a very nice result. In the areas of treatment the eruption had completely disappeared, and where there had been no treatment the eruption had persisted. About five years after that the disease recurred in a worse form and has been present ever since.

DR. MAURICE J. COSTELLO, New York: I don't know how often Dr. Blank administered 1,000 r of grenz rays to his patient. I think of keratosis follicularis as a light-sensitivity disease because every patient with it I have ever known who exposed himself to sunlight had an exacerbation of his eruption. If 1,000 r of grenz rays is given to any area on a patient with this disease, that patient is a candidate for radiodermatitis. I have seen a fair number of such patients in New York City.

DR. ANTHONY C. CIPOLLARO, New York: I should like to discuss several points: First, the evidence is overwhelming that this is a vitamin-deficiency disease. Secondly, as a manifestation of a vitamin deficiency, there is no rational basis for treatment of the disease by grenz rays, x-rays, or any other form of radiant energy. Thirdly, doses of 1,000 r of grenz rays will produce immediate erythema and hyperpigmentation, and later telangiectasis and maybe even atrophy, in that area; 1,000 r of grenz rays represents four times the erythema dose, and this dose is capable of producing telangiectasis some time in the future. Also, the evidence indicates that ultraviolet light will exacerbate the eruption. There is also evidence to indicate that patients receiving as little as 75 r to one area, using the conventional superficial x-rays, exhibit vesiculation. These should be sufficient grounds for avoiding all forms of radiant energy in treating patients with keratosis follicularis. An occasional patient may improve with very low voltage x-ray treatment, but, before advocating this form of therapy, let us thoroughly evaluate it on a rational and scientific basis.

DR. FRANK E. CORMIA, New York: This is a tragic case with a severe cosmetic defect, and to date none of the treatments has been of benefit. Not only has the eruption been worse in the summer months following exposure to sunlight, but in the last year and a half flare-ups have followed upper respiratory infections. The suggestion was made at the meeting of the New York Dermatological Society to give large doses of vitamin A by injection and, in addition, to try cortisone therapy. However, the rationale of the latter therapy is somewhat under question.

Leprosy, Lepromatous Type. Presented by DR. THOMAS N. GRAHAM, New York.

L. R., a Puerto Rican woman aged 25, is presented from Bellevue Hospital. She has been in the United States for five years. Two years ago she complained of recurrent epistaxis, obstruction of the nasal passages, malaise, fever, and paresthesias of the hands and feet, with

a loss of 15 lb. (6.8 kg.) in weight. Subsequently there appeared small painless nodules on the ear lobes, legs, face, trunk, and arms. During the past two years she received several courses of penicillin because of positive serologic reactions. Ten months ago the patient was admitted to Bellevue Hospital because of a painful erythematous tender nodular eruption of the legs and thighs.

Scattered over the arms, legs, and trunk are hyperpigmented and depigmented maculas interspersed with erythematous nodular tender lesions. The ulnar nerves are palpable. There is a perforation of the nasal septum.

Smears from an ear lesion, the nasal perforation, and an arm lesion were positive for acid-fast bacilli. The erythrocyte sedimentation rate was 35 mm. per hour. Results of other examinations were normal. A biopsy specimen was diagnosed as showing leprosy, lepromatous type.

During the patient's stay in the hospital the erythematous nodular lesions resolved with terramycin therapy but recurred soon thereafter. Treatment with sulfoxone sodium (diasone®) and "sulphetrone" (4,4'-bis[gamma-phenyl-N-propylamino diphenylsulfone-tetrasodium sulfonate], the present medicament) has not influenced the patient's condition. New nodular lesions continue to appear, and the patient has intermittent fever, malaise, and lassitude.

DISCUSSION

DR. FRANK E. CORMIA, New York: One canot assume that this patient's disease was not favorably influenced by the sulfone therapy. Lepromatous leprosy runs an extremely slow course. Dr. P. T. Erickson, of Carville, La., pointed out in a recent article that sulfone therapy must be continued over a long period, at times for five or more years. When the patient was first seen at Bellevue Hospital, she had a mild lepra reaction, which occurs in about 30% of cases. It is common to have more than one lepra reaction in lepromatous leprosy. After sulfone therapy, lepra reactions are frequent, but more than one is uncommon. Furthermore, Dr. Erickson noted that after sulfone therapy and the development of a lepra reaction, the disease may actually change from the lepromatous to the tuberculoid type. He stops treatment only if the lepra reaction has been very severe; if there is a mild reaction, he decreases the dose. I have had an opportunity to study a case of the so-called indeterminate leprosy. This patient had a severe ulcerative lepra reaction after four months' sulfone treatment. However, after further therapy the lesions have been undergoing involution satisfactorily; biopsies have shown a change from a nonspecific to a tuberculoid type of architecture, and the reaction to the lepromin test has become positive. The prognosis is not necessarily poor—it may be very good, but therapy has to be continued for a long time.

DR. ORLANDO CANIZARES, New York: The patient had "sulphetrone" for only several weeks; she had sulfoxone sodium for several months and showed several lepra reactions. I agree with Dr. Cormia that during a lepra reaction medication sometimes has to be discontinued until the reaction is over.

DR. ROBERT STOLAR, Washington, D. C.: During the past year three patients have been brought into Washington with leprosy. It was inferred that these drugs can be given for a short time and produce cures. That is not correct. It takes a very long time for treatment with these drugs to be effective. It is my belief that they do not have much effect on the bacterial invasion but that in some way they alter the immunity processes of the body. The number of organisms is slowly altered, and it may take months to three or four years for bacteriologic negativity to be achieved. If during administration of these drugs the patient displays exacerbations with a lepra reaction, one has to experiment with various doses of each drug to produce beneficial results.

DR. E. C. BARKSDALE, Washington, D. C.: Dr. R. A. Nelson is doing his treponemal immobilization test at the United States Naval Hospital, Bethesda, Md. I should like to ask Dr. Graham to send a specimen of blood to us.

DR. THOMAS N. GRAHAM, New York: Dr. Canizares has told you the length of time that "sulphetrone" was used. I agree that the only satisfactory treatment for leprosy is improvement of the patient's general condition.

Senear-Usher Pemphigus (Pemphigus Erythematosus). Presented by DR. GEORGE M. LEWIS, New York.

N. L., a woman aged 65, is presented from New York Hospital with an eruption of the face, scalp, and hands of four or five years' duration. In the summer while on vacation, she first exhibited a nonpruritic bullous lesion on the mid-forehead. Additional lesions on either side of the forehead soon developed, and the eruption lasted two or three weeks and then cleared spontaneously, leaving no trace. After two or three weeks the lesions reappeared, and then continued to come and go all summer, the first ones appearing at the sites previously involved, with more lesions developing on the forehead and cheeks. This pattern has been repeated over the years. Last year, for the first time, the patient had lesions on the scalp which persisted all winter. The scalp lesions are the only ones that have itched. Lesions appeared on the hands seven months ago and over the sternum in the past two weeks. The past history and family history are noncontributory.

The face and forehead are diffusely erythematous, with bullae 3 to 5 mm. in diameter on the forehead and over the top of the manubrium. There are several yellow-red crusts of similar size on the face, scalp, and backs of the hands. Nikolsky's sign was present on the forehead but not on the arm seven months ago, when the patient was first seen in this clinic, but it is absent now.

A patch test to 50% potassium iodide gave a negative reaction. The ultraviolet-light-sensitivity test showed no reaction at 30 in. (76.2 cm.) in 10, 15, and 20 seconds. The test for uroporphyrins gave a 3+ reaction on one occasion and a negative reaction on two occasions, including quantitative determination. Results of a routine urinalysis were normal; the white blood cell and differential counts were normal on three occasions.

Biopsy showed the epidermis to be essentially normal. There was a large subepidermal bullae filled with serum, throughout which round cells were seen. There was a dense infiltrate of a similar nature applied closely across the base of this bullae in a band-like fashion, which thinned out rapidly in the cutis below. The pathologic diagnosis was toxic subepidermal lesion, probably pemphigus.

The patient was given sulfapyridine, 1 gm. three times daily, with very good initial response. She lapsed during a vacation at the beach. She was given sulfadiazine and was doing well, but treatment was changed to meth-dia-mer-sulfonamides (terfonyl®), and she relapsed. She has continued to display new lesions in spite of a return to the use of sulfadiazine, 1 gm. daily.

DISCUSSION

DR. PAUL GROSS, New York: Since we have the benefit of Dr. Usher's presence, I should like to raise the question of the occurrence of mucous membrane lesions in the Senear-Usher type of pemphigus.

DR. B. USHER, Montreal, Canada: I believe the patient presents a typical example of this disease. I have not personally seen oral lesions in it, although Dr. Senear has described several instances. I believe the presence of erythematous bullous crusted lesions in a typical location and the chronicity of the eruption will bear out the diagnosis. I wish, however, to make a plea for the abolition of eponyms in connection with diseases. Neither Dr. Senear nor I wish to have our names perpetuated in this way. As a matter of fact, Dr. Ormsby deserved more recognition than he has received in this connection. The term pemphigus erythematosus is a more suitable one than that applied at the heading of this report.

DR. W. F. LEVER, Boston: There are two points against a diagnosis of pemphigus erythematosus. First, the reaction to the test for uroporphyrins was positive on one occasion and negative on two. Efforts should be made to decide definitely whether this patient excretes uroporphyrins. From a clinical standpoint it is conceivable that this patient has porphyria. The cutaneous lesions in chronic porphyria tend to become activated in the summer on exposure to the sun and often are bullous. The second point against a diagnosis of pemphigus erythematosus is that the bullae in this patient are subepidermal, whereas in pemphigus erythematosus they are invariably intraepidermal.

DR. DAVID BLOOM, New York: The eruption appears to me to be that of pemphigus erythematosus. In regard to what Dr. Lever says about subepidermal bullae, I cannot accept the view that the pathologist is justified in making a diagnosis of pemphigus according to the

location of the bullae. If he wishes to establish an objective criterion on the basis of examination of a series of cases, the clinical diagnosis in such cases must be agreed upon first by the clinician. I have found that not only does the pathologist rely on his ability to read the pathologic picture but he also has a tendency to be overconfident in his clinical observation.

DR. GEORGE M. LEWIS, New York: The question of nomenclature is interesting. From the prognostic standpoint we must realize that many of the patients with this disease eventually show pemphigus vulgaris, and, although this patient has had pemphigus erythematosus for many years, we cannot state that the outlook is unequivocally good. The finding of uroporphyrins is probably a red herring. Subequent determinations gave negative reactions, and we think the positive result was a technical error and would, therefore, throw it out. I presume I shall continue to be confused by the histologic interpretations of these bullous disorders and think we should not depend too much on what we hear from the pathologists regarding them.

Pemphigus Vulgaris Treated with Cortisone. Presented by DR. THOMAS N. GRAHAM, New York.

M. K., a Caucasian man aged 69, is presented from Bellevue Hospital with a generalized eruption of eight months' duration. In July, 1950, the patient exhibited painful lesions on the buccal mucosa and tongue, associated with much pain and numerous bleeding points. He was treated with hydrogen peroxide mouth washes, terramycin, and aureomycin without improvement. The penis showed a small ulceration at the corona glandis, observed in August, 1950. The tongue showed numerous erosions. The buccal mucosae also had some lesions which appeared to be ruptured bullae. The penis showed an ulceration 0.5 cm. in diameter on the dorsal coronal surface.

Results of urinalysis and a complete blood count were normal. A total of 4,000 mg. of cortisone was given in 24 days. For one week 100 mg. was given daily; the average dose was 200 mg. daily.

The oral lesions have healed 50 to 60%. The penile lesions have not changed, and the ulceration remains.

Pemphigus Vulgaris Treated with Cortisone. Presented by DR. J. GARDNER HOPKINS, New York (DR. ORLANDO CANIZARES, New York).

M. G., a Jewish man aged 60, from the Veterans Administration Hospital, Bronx, N. Y., was previously presented at a meeting of the New York Academy of Medicine. Between Feb. 14 and July 20, 1950, he was hospitalized at Presbyterian Hospital, New York, where he received several courses of corticotropin, 100 mg. daily, with less response to each course. He then received cortisone, with complete disappearance of all cutaneous lesions with a dose of 500 mg. daily between July 6 and 15, 1950. On his rehospitalization at the Bronx Veterans Administration Hospital on July 20, 1950, there were only a few scattered bullae and denuded areas. The skin was hyperpigmented, and there was decided "mooning" of the face.

There are some scattered bullae and denuded areas, with some crusting of the scalp. Pronounced hyperpigmentation and "mooning" of the face are present.

The patient has received various antibiotics as indicated for secondary infection, also frequent small transfusions. He has been given continual cortisone therapy since Aug. 2, 1950, for a total of 37.6 gm. through Feb. 16, 1951. Various schedules have been tried. The dosage necessary to prevent relapse has become gradually larger. As of Feb. 16, he was getting 200 mg. of cortisone orally and 100 mg. by injection daily.

Pemphigus Vulgaris Benefited by Cortisone and Corticotropin Therapy. Presented by DR. DAVID BLOOM, New York.

J. B., a man aged 67, exhibited a moderately pruritic bullous eruption on the trunk and extremities one month prior to his admission to the hospital (three months ago). On admission, Dec. 27, 1950, there were large flaccid bullae, broken bullae, denuded areas, and red plaques, remnants of previous lesions. There was mild involvement of the oral mucosa. The temperature was 102 F.

The blood chemical studies and blood counts gave normal results except for eosinophilia (9%). Fresh bullae showed 15% eosinophiles and old bullae 1% eosinophiles. The reaction to the potassium iodide patch test was 3+. Biopsy showed a subepidermal bulla; the histologic diagnosis was dermatitis herpetiformis or erythema multiforme bullosum.

Cortisone was given orally from Jan. 5 to 24, in doses of 200 to 400 mg. daily, a total of 4,600 mg. Corticotropin was administered from Feb. 1 to 13, in doses of 160 mg. daily for five days, 400 mg. daily for four days, 300 mg. daily for five days, and 250 mg. daily for three days, a total of 4,650 mg. Improvement was noticed a few days after administration of cortisone, but there was striking improvement with almost entire disappearance of bullae following large doses of corticotropin. At the time of the writing of this history (Feb. 17, 1951), no new bullae were seen.

DISCUSSION ON PRECEDING THREE CASES

Dr. W. F. Lever, Boston: I have recently reviewed the histologic sections from 65 patients with pemphigus. My findings agree with those of Civatte, first published in 1943 and since confirmed by French, Belgian, and English workers. In all patients with malignant pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, and pemphigus erythematosus, the bullae were invariably intraepidermal. In malignant pemphigus vulgaris, which we have been calling pemphigus vulgaris acutus and which is characterized by extensive oral lesions, flaccid bullae, and large areas of denudation, the bullae were predominantly suprabasal, i. e., occurring immediately above the basal layer. In pemphigus foliaceus and pemphigus erythematosus the bullae were located high up in the epidermis.

There is, however, another bullous disease which we have been calling pemphigus vulgaris chronicus and which is characterized by large, tense bullae, small erosions, and few, if any, oral lesions. In this disease the bullae are subepidermal. Whether this disease represents pemphigus or, as the French school believes, a bullous type of dermatitis herpetiformis is as yet undecided.

Dr. Maurice J. Costello, New York: This is a good time to give you briefly our experiences with cortisone and corticotropin therapy of pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. In private practice I have three patients with pemphigus, one of whom has been taking cortisone since March 10, 1950, in doses averaging 100 mg. daily. One is completely clear of all evidences of pemphigus; the disease in the other two patients is under control, and no new bullae have formed, but the lesions present have taken on a vegetative appearance.

Dr. Francis P. McCarthy, Boston: I believe the first case is one of bullous lichen planus rather than pemphigus vulgaris. The lesions are confined to the mouth except for several on the penis; they have been bullous at times, followed by erosions, and have suggested dendritic lesions of lichen planus. The fact that the lesions have been confined to the mouth for such a long period, even with the appearance of some on the penis, indicates to me the probability of bullous lichen planus. I have treated two patients with bullous lichen planus confined to the buccal mucosa, and in both the lesions followed auto accidents. Two or three days after the accidents the patients displayed oral lesions, primarily of the bullous type; as the disease progressed, typical lesions of lichen planus appeared. The microscopic picture of lichen planus was demonstrated, and it took six to nine months to clear up the lesions with bismuth therapy. To rule out lichen planus in this case, a biopsy should be performed from some of the dendritic lesions. There are several leucoplakic plaques on the lips which are consistent with lichen planus.

Dr. W. F. Lever, Boston: I am somewhat surprised at the poor results on treatment of this disease at Bellevue Hospital. At Massachusetts General Hospital, Boston, 13 patients with pemphigus have received corticotropin or cortisone therapy. Eight patients had pemphigus vulgaris, four pemphigus foliaceus, and one, pemphigus vegetans. Good results were obtained in all. It is extremely important that adequate doses are given. To most patients 200 mg. of corticotropin was given daily, but to several it was necessary to give 300 mg. With these doses new lesions usually ceased to form in pemphigus vulgaris and pemphigus vegetans within three to five days, while in pemphigus foliaceus the response was somewhat slower. The practice followed at present at Massachusetts General Hospital is to give large doses until the patient is

free of lesions, which usually requires three or four weeks. Then treatment is withheld until the disease becomes active again. Subsequent courses are given before the patient relapses severely; therefore, the duration of subsequent courses need not be long, usually one week to 10 days, but it is important to give large doses again. Treatment by small maintenance doses, for instance, 100 mg. of cortisone orally a day, has been found inadequate for suppression of the disease. It is our feeling that patients with pemphigus usually show no improvement on treatment with corticotropin or cortisone unless the eosinophile count at the height of the effect of the drug is depressed to a level below 50 per cubic millimeter. Of our 13 patients with pemphigus, 8 are at present free or practically free of lesions; 2 have a small number of lesions not requiring re-treatment at present, and 3 are being re-treated. It is interesting that after treatment with large doses the remissions often are prolonged. The longest remission so far was seven months.

DR. GEORGE C. ANDREWS, New York: We are not as pessimistic as Dr. Costello is, although he did have one patient who was cured. We have one patient who has been free of lesions and back at work for many months now with administration of 100 mg. of cortisone twice a week, but, on the whole, I feel that our experience has been between that of Dr. Costello and that of Dr. Lever. We have had some deaths, thought to be due to inadequate doses. I do think the drug prolongs the disease and makes it possible for these patients to live longer. They are still suffering from pemphigus, although remissions may last a considerable period. On the whole, it is remarkable to see a person one doesn't expect to live more than 24 hours, with severe pemphigoid mouth lesions, bullae all over, high erythrocyte sedimentation rate, and high fever, after adequate dosage of cortisone or corticotropin display a sense of well-being and come back to life. These patients vary a great deal in responsiveness and the dosage necessary. It will perhaps take several years to find out just how valuable these hormones are.

DR. ORLANDO CANIZARES, New York: At the Veterans Administration Hospital we have treated three patients, and I think cortisone saved the lives of two, who are now almost entirely well. In one patient the condition is under control with a maintenance dose of 100 mg. a day. The third had a fulminating type of the disease and died.

DR. HARVEY BLANK, Philadelphia: A child hospitalized with severe infantile eczema was treated cautiously with corticotropin and responded to the first course. Subsequently, the dose had to be increased to 50 mg. a day to maintain a remission. [Dr. Blank presented slides showing gangrene of the wrist, including the entire left hand, of the peripheral end of the toes, of the tips of the ears, and of the back of the head.] Cortisone was applied locally without effect and then was given systemically in a dose which was gradually increased to 65 mg. a day. This was decreased over a four- or five-day period by halving the dose. Ten days after the last dose the child looked perfectly normal and then went into shock and remained in shock for 24 hours. Although we thought the adrenal cortex had been damaged, we were surprised to find the blood chemical values, including those for chlorides, normal. The only explanation offered was that an increased coagulability of the blood, combined with shock, produced intravascular thrombosis in the small vessels farthest from the heart. We had thought that if there were any adverse reactions, such as cardiac arrhythmia and glycosuria, from these drugs, they would be reversible, but we learned to our sorrow that irreversible reactions can be produced. We, therefore, recommend extreme caution in the use of these drugs except in diseases with a serious prognosis.

DR. DAVID BLOOM, New York: The effect of corticotropin in this patient, who came in moribund and with an eruption typical of pemphigus vulgaris, was dramatic, and there is no doubt in my mind that use of this drug has prolonged his life, although the final outcome is by no means certain. I feel from my previous experience with the treatment in pemphigus vulgaris that this drug is the best we have at our disposal for pemphigus therapy.

Lupus Erythematosus (Discoid?) Treated with Cortisone. Presented by DR. J. GARDNER HOPKINS, New York.

P. J. D., a man aged 27, is presented from the Vanderbilt Clinic, New York, with an eruption on the face and ears of three years' duration. This began as a pimple on the nose, and subsequently numerous plaques developed on the face and ears. There are no systemic symptoms and no light sensitivity. Results of the general physical examination are normal.

On his admission to the clinic covering the entire nose and extending slightly onto the cheeks was a large erythematous slightly infiltrated plaque covered with adherent scales, with plugs running into the follicles. Ten smaller plaques 3 to 22 mm. in diameter were seen on the forehead, cheeks, and ears, with larger plaques in the postauricular folds. There was slight silvery scaling on the vermilion borders of the lips.

On admission the erythrocyte sedimentation rate was 70 mm. per hour and on discharge 65 mm. On admission the hematocrit reading was 39%; the hemoglobin concentration was 12.4 gm. per 100 cc., and white blood cells numbered 5,300, with 71% polymorphonuclear leucocytes, 24% lymphocytes, 2% monocytes, and 1% eosinophiles. On discharge the hemoglobin concentration was 12.6 gm. per 100 cc.; red blood cells numbered 3,900,000 and white blood cells 6,800, with 85% polymorphonuclear leucocytes and 15% lymphocytes. The serum proteins were 7.2 gm., with 4.8 gm. of albumin and 2.4 gm. of globulin. Sodium measured 132 mEq. per liter, potassium, 4.1 mEq., and carbon dioxide content, 26.8 mEq. Urea nitrogen was 23 mg. per 100 cc. No L. E. cells were seen on incubation of the normal buffy coat with the patient's serum. The VDRL slide showed a positive result in 2 dilutions; the Mazzini reaction was doubtful; standard Kahn and Kolmer tests gave negative reactions. The result of the treponemal immobilization test was negative, and a roentgenogram of the chest was normal. An electrocardiogram showed right bundle branch block and myocardial change believed due to basic disease. A biopsy specimen was diagnosed as showing lupus erythematosus.

Cortisone acetate was administered, 300 mg. the first day, 200 mg. the second day, and 100 mg. daily for 43 days (to Feb. 12). A slight decrease in erythema occurred in 24 to 48 hours, and a gradual but very slow diminution was noted in scaling, erythema, and infiltration for the successive six weeks. Treatment was then changed to gold sodium thiosulfate administration. At the end of cortisone treatment the lesions appeared as faintly erythematous spots without perceptible infiltration or scaling. The smaller lesions had disappeared, and the nose lesion had greatly decreased in size.

Chronic Discoid Lupus Erythematosus Improved with Cortisone Therapy. Presented by DR. MAURICE J. COSTELLO, New York.

H. A., a man aged 36 in apparent good health, has had for many years on the face, nose, and back a number of discoid scaly erythematous telangiectatic atrophic lesions of varied size and configuration.

Results of urinalysis and blood count were normal. Microscopic examination of skin sections revealed characteristics consistent with lupus erythematosus of the chronic type.

Treatment has consisted of administration of gold salts, bismuth subsalicylate, vitamins and parenterally, crude liver extract and refrigeration with solid carbon dioxide, with little beneficial therapeutic effect. Cortisone, 200 mg. daily, was administered orally, to a total of 4,800 mg. The lesions of the face, but not those on the skin of the back, show improvement in that there has been a decrease of erythema and scaling.

Epidermolysis Bullosa Acquisita Treated with Corticotropin. Presented by DR. MAURICE J. COSTELLO, New York.

J. K., a man aged 42, is presented from Bellevue Hospital with an eruption on the elbows, wrists, hands, knees, ankles, feet, buttocks, and medial aspect of the thighs, of 10 years' duration. In January, 1940, the patient noticed itching, and this was followed by the appearance of vesicles and bullae.

The locations mentioned are covered with straw- to blood-colored bullae of varying sizes and stages of involution and evolution. A number of lesions are infected and ulcerated. The bullae are produced by trauma, usually not by a blow directly at right angles to the skin but by a glancing blow. Nikolsky's sign is present.

Tests of the urine showed albumin (trace). The red blood cells were 4,050,000 and white blood cells 13,100. The blood nonprotein nitrogen was 30 mg. per 100 cc., cholesterol 250 mg., albumin 4.5 gm., and globulin 2.2 gm. The appearance on biopsy was consistent with epidermolysis bullosa.

Treatment, other than hospitalization and bed rest, has been of little avail. He has received vitamin C, crude liver extract, and general supportive treatment. The patient had a long spontaneous remission from 1943 to 1946. Corticotropin, 1,000 mg., was administered by intramuscular injection from Dec. 1 to 10, 1950. New bullae occurred on the fourth day of treatment, but no lesions appeared for the next week. However, new bullae appeared when corticotropin therapy was discontinued. Beginning Jan. 30, 1951, corticotropin was administered in doses of 200 mg. daily for three days, during which no new bullae occurred. Readministration from Feb. 4 to 10, in doses of 200 mg. daily, did not cause old lesions to heal, but they did heal promptly when penicillin was administered, 600,000 units daily. A total of 2,600 mg. of corticotropin was given. The patient was rather euphoric during the course of therapy with corticotropin.

Lupus Erythematosus Disseminatus Acutus (Systemic) Treated with Corticotropin and Cortisone. Presented by DR. MAURICE J. COSTELLO, New York.

C. P., a Peruvian man aged 28, is presented from Bellevue Hospital with an eruption of five or more years' duration involving the face, ears, neck, upper part of the chest and back, external aspects of the arms, elbows, forearms, hands, and knees. The patient has mild to moderate constitutional symptoms, such as fatigue, loss of weight and appetite, pains in the muscles and joints, and fever. An exacerbation and extension of the eruption occurred eight months ago after prolonged exposure to mountain sunlight in Peru.

There is a dull, erythematous edematous scaly eruption which almost covers the entire face, neck, and chest. The lesions on the back and extremities consist of macules and small scaly papules which have not coalesced and are of lighter hue than the lesions on the face. The left index finger is covered with numerous pinpoint erythematous macules and papules. The hairy part of the scalp shows diffuse erythema with a moderate amount of alopecia. This eruption probably began as the discoid type of lupus erythematosus, as evidenced by the scarring on the right side of the bulbous portion of the nose, although some of this punctate scarring was caused by surgical diathermy.

Urinalysis showed a trace to 1+ reaction for albumin, with 8 to 10 hyaline casts. The erythrocytes were 3,350,000 and leucocytes 3,300, with 42% polymorphonuclear leucocytes, 54% lymphocytes, and 4% monocytes. The thrombocyte (platelet) count was 255,000 and the erythrocyte sedimentation rate 21 mm. per hour (Wintrobe). The nonprotein nitrogen of the blood was 32 mg. per 100 cc., cholesterol 195 mg., albumin 3.8 gm., globulin 3.1 gm., and sodium chloride 100 mg. The cephalin-flocculation test gave a slightly positive reaction; the electrocardiogram and the roentgenogram of the chest were normal. On second examination of the peripheral blood, the L. E. cell was found. A biopsy specimen taken on Dec. 11, 1950, showed lupus erythematosus (subacute).

Corticotropin, 100 mg. daily for 20 days, was given, to a total of 2,000 mg. During this period the facial eruption faded, but the eruption on the arms and chest remained unchanged. On the 20th day of therapy new macules appeared on the palmar aspects of the tips of the fingers and on the palms. Cortisone was given for 11 days recently, 200 mg. daily. During this time the patient had mild anginal pains, and use of the drug was discontinued for five days. New macules appeared on the face, and the erythema returned. The therapeutic result was considered poor.

DISCUSSION ON PRECEDING FOUR CASES

DR. FREDERICK G. KALZ, Montreal, Canada: Of all the conditions treated in Montreal with this method, this disease showed the most gratifying results, but there are some difficulties, and I should like to hear what the members think about them. Should we or should we not combine this therapy with antibiotic administration? We have had great difficulty because of changes in the intestinal flora, avitaminosis, and monilial infections. There is also a tendency to severe coccal infections, and we lost two patients in this way.

DR. GEORGE C. ANDREWS, New York: We have found treatment with cortisone and corticotropin beneficial in the discoid type of lupus erythematosus. Its advantages are, of course, well established in the disseminated type, but it is not as beneficial in the discoid variety because

relapse occurs when administration of the drug is stopped. With cortisone therapy we have been able to clear up extensive lesions that had not responded to any of the established remedies. The dosage has not been high. I think that with cortisone reactions can be largely prevented by giving smaller doses. The infant mentioned earlier was getting 50 mg. daily, which is a huge dose for a child. We should examine the coagulability of the blood more frequently. Some patients have thromboses or gangrene. With lupus erythematosus of the discoid type, there is no doubt that in some of the cases there are changes that make one wonder what the borderline is between discoid and disseminated types. Some of the patients with the discoid type, in addition to marked leucopenia, will show a high sedimentation rate; therefore, it is possible that they have a more generalized involvement than is apparent.

Dr. M. M. Tolman, Boston: I wish to report one case of discoid lupus erythematosus with subacute manifestations, first seen years ago. Remission was brought about by gold sodium thiosulfate therapy and was maintained. With the coming of corticotropin and cortisone, the patient succeeded in getting himself admitted to a Veterans Administration Hospital, where he received corticotropin and cortisone. After he was out of the hospital three weeks, he came back again with a subacute lupus erythematosus and marked bilateral gynecomastia.

Dr. Orlando Canizares, New York: It is generally believed that cortisone is a specific for disseminated lupus erythematosus, but Dr. Costello mentioned that the therapeutic results were poor in his case. I think any other patient would have improved as much after staying two or three months in the hospital, even without medication. I want to mention an experiment undertaken at the Veterans Administration Hospital with the local injection of cortisone in lupus erythematosus and psoriasis. Five milligrams per cubic centimeter was injected locally into the lesions with no improvement.

Dr. Maurice J. Costello, New York: We have treated three patients with lupus erythematosus of the acute disseminated type; one showed poor results, one showed fair results, and one died. In four patients with lupus erythematosus of the discoid type, improvement was always spectacular at the beginning of treatment, but, when cortisone therapy was discontinued or the dose decreased, they were worse than when the treatment was started. In patients with discoid lupus erythematosus of the disseminated type, we have had fair results with cortisone treatment; the lesions on the extremities have not recurred, although the lesions on the face are about the same. I will sketch some of the toxic reactions so far. A patient with polycythemia vera had a universal eruption of the exfoliative type which cleared with cortisone therapy. Abdominal pain developed, he died, and the cause was not determined at postmortem examination. One patient with urticaria of 25 years' duration showed spectacular improvement in the first two weeks and then had persistent headache suggesting brain tumor. Four patients exhibited symptoms indicating intermittent claudication, and one had a bilateral lumbar sympathectomy to relieve her condition. One patient with dermatomyositis died of adenocarcinoma of the ovary, with dissemination of the cancer all over the body in a rather wild manner. This patient had been examined seven months before at a cancer-detection clinic, and no evidence of cancer had been found. A patient at Bellevue Hospital with psoriasis arthropathica died in uremia. Two patients displayed mental depression, of a severe type in one. A private patient who had severe pemphigus vulgaris is now well; demineralization of the vertebrae developed, with spontaneous fractures of three vertebral bodies. I rarely have seen a patient with pemphigus vulgaris acquire decubitus ulcers; however, not only did several patients receiving cortisone therapy have bedsores but the ulcers did not heal until use of the drug was discontinued. In the dermatologic service at Bellevue Hospital a patient receiving large doses of corticotropin had thrombosis of both popliteal arteries and gangrene of the lower extremities.

Case for Diagnosis: Angioblastoma? Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi? Presented by Dr. Anthony C. Cipollaro, New York.

P. T., a man aged 70, was first seen in the dermatology department of the New York Polyclinic Medical School and Hospital on Jan. 15, 1951. Two years previously he first noted a painless swelling in his left groin which was subsequently accompanied with swelling of his left leg. About one year ago he became aware of two small reddish nodules on the lateral aspect of his left foot which increased slowly in size and bled intermittently. Two months ago a

nodule appeared in the midline of his forehead; this is painless and has not grown. During the past two weeks he has had polyuria, urinating 10 to 15 times a day. In 1912 he had a fracture of his left ankle, and in 1934 he had a right inguinal hernia repaired.

There is a hard, movable, painless mass in the left inguinal area which measures 10 by 15 cm. Below this, on the lateral surface of the left thigh, there is diffuse telangiectasia, with some purpura and nonpitting edema below the knee. Directly below the left lateral malleolus is a dark-red nodule with some granulation tissue and exudation. It measures about 1 cm. in diameter. A similar lesion about 4 cm. in diameter is just anterior to the smaller lesion. Biopsy specimens were taken from both lesions. On the forehead just about at the midline is a painless ovoid mass which measures 3 by 3 cm. It appears to be soft and subcutaneous. There is also a raised red soft lesion about 0.5 cm. in diameter on the left buccal mucosa. This has the appearance of a small angioma.

The blood count shows 4,250,000 red cells, 13.8 gm. of hemoglobin per 100 cc., and 6,300 white cells, with 64 polymorphonuclear leucocytes, 28 lymphocytes, and 8 monocytes per 100 cells. Results of the urinalysis were normal, and reactions to serologic tests for syphilis were negative.

The biopsy of the anterior nodule showed granuloma pyogenicum and that of the posterior nodule showed angioblastoma (probably Kaposi's sarcoma [multiple hemorrhagic hemangioma of Kaposi]).

DISCUSSION

Dr. Francis A. Ellis, Baltimore: Hemangioendothelioma would certainly explain the rapid progress, and I think the histologic picture with the large uniform type of cell is compatible with that diagnosis.

Dr. Perry Sachs, New York: Hemangioendothelioma is a term similar to and often synonymous with angioblastoma. Some authors have thought it might fit in with Kaposi's sarcoma, rather than under the broader classification of angioblastoma. The sections from the lesion, after it was excised by the surgeons, were more typical of Kaposi's sarcoma than were the original biopsy sections. The interesting feature is the presence of large multinucleated cells in the lymph node. This suggests lymphoblastoma, possibly Hodkgin's disease. There are reports of the coexistence of lymphoblastoma and Kaposi's sarcoma.

Dr. Anthony C. Cipollaro, New York: This clinical picture is a very confusing one. It is not a typical clinical example of Kaposi's sarcoma. When the patient was first seen, he had a small lesion on one ankle which appeared to be granuloma pyogenicum; as a matter of fact, that was the pathologist's opinion, but he couldn't explain the tremendous mass in the groin. This mass was removed, and it was thought by the dermatopathologist and even by the general pathologist to belong to the Hodgkin group. So even now we don't have a clear histopathologic picture and certainly not a clear clinical picture. I am afraid we shall have to await further developments, which will perhaps be at the autopsy table. We have not explained the tumor on the forehead. We don't know whether the patient has a growth within the abdomen, retroperitoneal area, or thoracic cavity. The findings on all examinations fail to support any one concept.

Generalized Dermatophytosis Due to Trichophyton Rubrum. Presented by Dr. George M. Lewis, New York.

DISCUSSION

Dr. George M. Lewis, New York: The reaction to Trichophytin in these patients is evidenced in more than 50% by an immediate wheal formation. This is sometimes of valuable diagnostic help. We are apt to use the Trichophytin test too infrequently in our routine work, and this is one time when it may be of decided value.

Bullous Dermatosis Associated with Hyperglobulinemia, Proteinuria, and Plasmocytosis of Bone Marrow; Drug-Sensitivity Reaction(?); Multiple Myeloma(?). Presented by Dr. Orlando Canizares, New York.

H. B., a man aged 55, was previously presented before the Manhattan Dermatologic Society from the Veterans Administration Hospital, Bronx, N. Y.

The patient had pneumonia in January, 1950, treated with penicillin, sulfamerazine, and sulfadiazine. In July, 1950, he had an attack of nausea, abdominal cramps, and diarrhea and was told that he had a kidney infection and that there was protein in the urine. He was given sulfisoxazole (gantrisin®), 0.5 gm. three times daily, from July 9 to Sept. 5. On July 11 bullae began to develop and have continued to develop to date, although they are less numerous now. The patient has been studied elsewhere, and diagnoses of multiple myeloma and pemphigus were entertained. A course of corticotropin therapy, 520 mg. in 13 days, did not alter the course of his illness at that institution.

A test dose of succinylsulfathiazole (sulfasuxidine®), given two months ago when only one or two bullae were appearing daily, was followed by rapid increase in the number of bullae in 24 hours. At present bullae are appearing at the rate of one or two a day on the backs of the hands and feet and in the shaving area of the beard. He feels well otherwise. There are now a few bullae or denuded areas on the dorsa of the hands and feet.

There were 3,500,000 red blood cells and the hemoglobin concentration was 11.8 gm. per 100 cc. White blood cell and differential counts were normal. The erythrocyte sedimentation rate was 35 mm. per hour. Urinalysis showed a 4+ reaction for protein, with some granular and hyaline casts. Globulin was present in the urine, but there were no Bence Jones proteins. Uroporphyrins were not found. Urea clearance was 100% in the first specimen and 88% in the second. The blood urea nitrogen was 17 mg. and total cholesterol 236 mg. per 100 cc. The Congo red test showed 74% dye retention in the serum after 45 minutes. The total blood protein varied from 7.2 to 7.8 gm., with 2.4 to 2.8 gm. of albumin and 4.8 to 5.2 gm. of globulin, per 100 cc. Serum electrophoretic studies showed the alpha globulin to be elevated, with gamma globulin at the upper limit of normal. Examination of the bone marrow disclosed plasmocytosis (38.5%) and 5% plasmoblasts, observations which were reported as consistent with a diagnosis of multiple myeloma. The appearance of a skin biopsy specimen was consistent with pemphigus or epidermolysis bullosa. All bones were normal on roentgen study.

DISCUSSION

DR. DAVID BLOOM, New York: I believe that in this case the epidermolysis bullosa is not hereditary but acquired from irreversible damage to the skin by previous long administration of sulfonamides. I have observed several such cases of sulfonamide-produced epidermolysis bullosa; they start with a generalized bullous eruption which gradually assumes the features of epidermolysis bullosa.

DR. W. F. LEVER, Boston: The diagnosis of multiple myeloma seems to me very unlikely. I do not know of a case of multiple myeloma in which there were cutaneous lesions. Aside from that, Bence Jones protein should be present either in the urine or, if not excreted, in the blood serum, in which case it could be seen in the electrophoretic pattern.

DR. GEORGE C. ANDREWS, New York: I have always admired the work of Dr. Bloom on the pemphigoid eruptions caused by the sulfonamide drugs, and I think his explanation may be a proper one here—the condition may be epidermolysis bullosa caused primarily by the sulfonamides. I have two patients with pemphigus which followed the prolonged use of sulfonamides.

DR. ORLANDO CANIZARES, New York: I believe Bence Jones proteins are found in the urine of only approximately 65% of the patients with multiple myeloma.

Sarcoidosis. Presented by DR. LESLIE P. BARKER, New York.

Case for Diagnosis: Sarcoid-Like Lesions on Face; Facial Granulomas? Presented by DR. NATHAN SOBEL, New York.

Incontinentia Pigmenti (?) Associated with Hydrocephaly. Presented by DR. J. LOWRY MILLER, New York.

Erythema Multiforme Vs. Periarteritis Nodosa Treated Successfully with Corticotropin (ACTH). Presented by DR. MAURICE J. COSTELLO, New York.

Pseudoxanthoma Elasticum. Presented by DR. MAURICE J. COSTELLO, New York.

Case for Diagnosis: Periarteritis Nodosa? Presented by DR. ORLANDO CANIZARES, New York.

Chronic Double Generalized Mycosis (Epidermophyton Floccosum and Candida Albicans). Presented by DR. ORLANDO CANIZARES, New York.

Facial Granuloma with Eosinophilia. Presented by DR. SAMUEL M. PECK, New York.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Paul Gross, M.D., *Chairman*

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March 6, 1951

Superficial Basal-Cell Epitheliomatosis; Ulcerating Basal-Cell Epithelioma with Anaplastic Change; Plantar and Palmar Hyperkeratosis. Presented by DR. J. AMERSBACH.

L. S., a man aged 55, was admitted to the dermatological service of the New York Polyclinic Medical School and Hospital on March 5, 1951. When he was 10 years old, a superficial scaling lesion appeared on the anterior surface of the right leg. It was diagnosed as psoriasis, and he was given arsenic preparations by mouth and locally, without results. When he was 30, this lesion was about the size of a silver dollar and became ulcerated. It changed little until about 15 years ago, when the patient was working in a factory and exposed to fumes of a grease solvent, at which time the lesion gradually increased to about 3 in. (7.6 cm.) in diameter. During the past four months it has grown rapidly and become much deeper.

About seven years ago the patient noticed a pruritic, scaling lesion on the right chest which enlarged slowly and two years ago became nodular. Also seven years ago he noted a "sore pimple" in his left groin which slowly enlarged, and during the past four months it has become ulcerated and granulomatous. Hyperkeratosis has also been present for seven years.

The patient had jaundice at the age of 17 and has been treated for generalized neuritis and optic neuritis recently with vitamin B. His grandmother had a localized skin cancer of the forehead.

Located on the anterior surface of the right leg is a granulomatous ulcer 13 by 10 cm., with an infiltrated border. Just below the left inguinal ligament is a raised, sharply marginated, granulomatous tumor 3 by 8 cm., with a glistening surface. On the upper right chest above the mammary gland is a large, rounded, deep red tumor, in the center of which is a raised nodule about 1 cm. in diameter. Numerous superficial erythematous scaling lesions of varying sizes can be seen on the trunk, occiput, left arm, legs, and left sole. There is no lymphadenopathy. Plantar and palmar hyperkeratosis is present.

A biopsy specimen of the large ulcerating lesion on the right leg showed an infiltrating basal-cell epithelioma with beginning anaplastic change.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: I am impressed with the multiplicity of the lesions that have resulted from one etiological agent—arsenic. If you look at the flat lesions under the light, you can detect a thread-like border along the periphery, as in the gumma-like lesion on the right chest, which fits in with the original description of Bowen and with the large ulcers in the left groin and on the right leg. Obviously, different lesions require different methods of treatment. Just what to do about the large lesions on the legs is a problem; perhaps the answer would be excision, followed by full-thickness skin grafting. If I were responsible for this patient, before proceeding I would discuss with a plastic surgeon the feasibility of removing this large mass and replacing it with fresh skin from some other part of the body. It is also remarkable that the patient has had this lesion on the right leg for 15 years with no evidence of metastasis. When the patient was first seen, the lesion was thought to be a basal-cell epithelioma, but biopsy showed a basal-cell lesion with anaplastic cell changes. If it were a squamous-cell epithelioma, one would expect metastases to be present after 15 years.

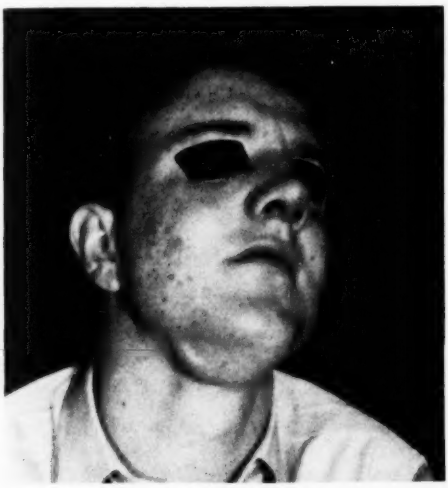
DR. GEORGE M. LEWIS: It would be well to advise this man against amputation. If this patient were observed and studied by some of the radical-minded surgeons, he might be told that his leg should come off in order to save his life, but I disagree. It doesn't matter much whether the lesion is excised or removed by electrosurgical methods, but I think he should be advised against amputation.

DR. PAUL GROSS: This condition used to be called superficial benign epitheliomatosis of Little. Ayers and Anderson were the first to show that in some of these cases there are evidence of arsenical keratosis and a history of chronic arsenic retention. This explains why anaplastic changes occur not infrequently.

DR. PERRY SACHS (by invitation): By anaplastic changes we mean that the basal cells have changed in character so that they are larger and have more cytoplasm. Also, the nuclei are larger and rounder and usually stain more deeply. In other words, they are more like the cells seen in Paget's disease or nevocarcinoma (melanoma). Although they may not attain that degree of alteration, they approach such a stage. This change indicates a more malignant lesion than the usual superficial basal-cell epithelioma. Clinically, the patient's lesion corroborates such an observation.

Sporotrichosis Involving the Face. Presented by DR. ANTHONY C. CIPOLLARO for DR. JOSEPH I. SINGER, Bay Shore, N. Y.

H. K., a youth aged 20, first examined March 1, 1951, immigrated to the United States from Holland one year ago. His first job was in a nursery. Early in January, 1951, the patient had



Sporotrichosis of face.

a swelling of the neck and an eruption on his nose. Both lesions have been progressing. Except for acne for the last year, the past medical and dermatologic history was normal. Since January, the patient has received two penicillin injections and aureomycin for this condition, without relief.

On the medial and superior aspects of the right naris, there is a keratotic and verrucous patch of dermatitis. From this patch a chain of small deep nodules descends to a cystic submental swelling and larger, firm nodules (Figure). There is no apparent systemic reaction.

On March 1 several cubic centimeters of serosanguineous fluid was aspirated from the cystic mass and streaked on Sabouraud's dextrose medium. The first growth was noticed in four days as tiny, white, filamentous colonies. A culture mount made today (March 6) revealed a fine branching mycelium with lateral pyriform to round microconidia. Smears of the pus have not yet been stained.

DISCUSSION

DR. GEORGE M. LEWIS: I should like to congratulate the presenter, first of all, for thinking of the possibility of this disease in an unusual location and, second, for presenting a culture which is showing just sufficient characteristics that one can be certain that the growth is Sporotrichum

schenckii. What might be considered lymph nodes are probably nodules, and this again illustrates the rarity of involvement of the lymph nodes in this disorder. The prognosis is good, although the fairly rapid spread in a rather short time makes one hope that treatment will be undertaken without delay. Potassium iodide is probably still the best treatment.

DR. ANTHONY C. CIPOLLARO: Dr. Singer has been practicing dermatology in the central portion and south shore of Long Island for only about two years, and in that time he has encountered six or seven cases of sporotrichosis, which is amazing. I have practiced here in New York for a long time without seeing a case. Most of these cases he has been able to trace to hay used for protecting tulip bulbs in that section of Long Island.

DR. JOSEPH I. SINGER (by invitation), Bay Shore, N. Y.: This is the sixth case I have seen in about 14 months. I should hesitate to present this patient if he had the chancre of inoculation on the finger, but since the site and the appearance—a verrucous lesion—were unusual, I thought the case would be of interest. The patient works with tulip bulbs, and four of the six patients gave a history of coming into contact with hay, which is stacked every summer and used every winter to cover the bulbs. With the chain of nodules along the lymphatics and the fluctuant abscesses, I thought there was a good chance of the condition's being sporotrichosis; therefore, I aspirated fluid and inoculated it and yesterday could first identify the growth as typical of the Sporotrichum organism. I began the administration of potassium iodide last night in small doses which will be increased. All the patients have shown a number of nodules with extensive involvement, and all have responded well to potassium iodide.

Lupus Vulgaris. Presented by DR. EMORY LADANY.

DISCUSSION

DR. EMORY LADANY: The patient was presented for two reasons: first, because of the rather extensive involvement (nose, cheeks, legs, neck) which is not often seen in this country, and, second, for the therapeutic result. The patient was given vitamin D_2 for a year without benefit. When she first came to this country from Hungary about 18 months ago, she was given 150,000 units of vitamin D_2 together with ultraviolet irradiation and showed a very poor result, as only about 20% of the lesions involuted. Last summer, after a year's treatment, I gave her 42 gm. of dihydrostreptomycin, two injections of 0.5 gm. daily, whereupon she showed a wonderful result in about two weeks. Half the lesions disappeared, and after discontinuance of therapy almost all the lesions were gone. The lesion on the nose was present when I first saw the patient, and I thought of basal-cell epithelioma but didn't want to take a biopsy specimen for cosmetic reasons. However, I coagulated the lesion on two occasions and believe this will lead to healing. Preceding the dihydrostreptomycin therapy, I gave *p*-aminosalicylic acid; the patient tolerated it for a while but then couldn't take it any longer. After the dihydrostreptomycin treatment, calciferol was administered again, and she tolerated it for a while. Now most of the lesions are well cleared, and the site of the basal-cell epithelioma after coagulation should heal in a short time.

Macular Atrophy (Schweninger-Buzzi Type); Chronic Discoid Lupus Erythematosus. Presented by DR. ANTHONY C. CIPOLLARO.

H. K., a woman aged 37, is presented from the New York Polyclinic Medical School and Hospital with an eruption on the face, arms, and axillary folds of eight years' duration. The lesions on the arms began as small oval erythematous maculas, which gradually enlarged and rose above the skin surface. After varying periods the skin has become soft, white, and wrinkled. These areas then herniate and assume bladder-like formations. This process is still occurring. The lesions on the face become prominent in the warm weather as raised, erythematous, sharply marginated plaques. All lesions are symptomless.

At the age of 4 years the patient was operated upon for an infected gland thought to be tuberculous. In 1941 she had pleurisy and a shadow in the apex of the right lung. She was observed for two years with roentgenographic examinations, without eliciting evidence of tuberculosis.

On the arms laterally and medially, on the flexor surfaces of the forearms, and about the anterior and posterior axillary folds are pea- to silver-dollar-sized white and erythematous lesions in which the skin is soft and wrinkled and can be herniated slightly. On the right arm laterally is a tumorous lesion about 3 cm. in diameter, which is raised in the center, has a sloping border, and feels soft and lipomatous on palpation. The hair follicles are much dilated in all these lesions. On the central part of the face are raised, slightly marginated, erythematous plaques. On palpation these have very little infiltration, and the erythema disappears on diascopic pressure.

The blood study shows 12 gm. of hemoglobin per 100 cc. and 3,980,000 red blood cells and 6,800 white blood cells per cubic millimeter, with 67% polymorphonuclear leucocytes, 26% lymphocytes, 4% eosinophiles, and 3% monocytes. Results of urinalysis were normal, and the Kahn reaction of the blood was negative. The results of the tuberculin test and roentgenogram of the chest have not yet been reported.

A biopsy revealed the blood vessels to be dilated throughout the upper cutis, with a mild focal reaction of small round and wandering connective tissue cells. The cutis showed pronounced edema. There were no significant changes in the epidermis. The elastic tissue was missing throughout the upper cutis. The diagnosis was macular atrophy.

Another biopsy specimen showed great edema of the cutis, dilated blood vessels, and a focal reaction composed of small round and wandering connective tissue cells. The epidermis was thin and flattened, with somewhat dilated and plugged follicles. There was little cutis present, and fat could be seen higher up in the section. The elastic tissue was clumped in the subepidermis. The diagnosis was atrophic process; lupus erythematosus could not be ruled out.

DISCUSSION

DR. LOUIS CHARGIN: There is no question of this being macular atrophy of the Schweninger-Buzzi type. This case furnishes occasion to discuss the question whether Schweninger-Buzzi disease is a primary macular atrophy. What Schweninger and Buzzi described was an end-process exhibiting atrophy, and the original lesion, whatever it may have been, had not been determined; hence, all we can say is that Schweninger-Buzzi disease presents atrophy differing in no way from the secondary macular atrophy seen in the wake of syphilis, tuberculosis, etc. Accordingly, at this time we must look upon Schweninger-Buzzi disease not as a primary process but as a secondary one; hence we can regard all cases of secondary atrophy as types of Schweninger-Buzzi disease.

There is, however, a primary macular atrophy *sui generis*. I refer to the Jadassohn anetoderma. This process begins with a lesion peculiar to the disease and terminates in macular atrophy. In this disease, too, the end-stage differs in no way from secondary macular atrophy.

DR. E. T. BERNSTEIN: In Schweninger-Buzzi disease there is a plaque-like atrophy, anetoderma. The question arises whether there is such a thing as primary atrophy. The conception of the disease was revised; it is now considered a sequel of something preexisting. Is there a connection between chronic discoid lupus erythematosus and Schweninger-Buzzi macular atrophy? Perhaps there is, and the disseminated, very superficial patches of lupus erythematosus of the discoid type have resulted in such an atrophy.

DR. GEORGE M. LEWIS: I should like to suggest that the lupus erythematosus is of the seborrhea congestiva type rather than the discoid, as labeled. I doubt that there will be any residual atrophy when the lesions undergo involution, and the prognosis is much better than with the discoid type.

DR. PAUL GROSS: I presented a similar case before the most recent Atlantic Dermatological Conference. The patient had many large lesions of the Schweninger-Buzzi type of macular atrophy, together with several lesions of the face resembling lupus erythematosus. The biopsy specimen from a facial lesion showed only simple inflammatory changes, ruling out lupus erythematosus. I agree with Dr. Chargin that there is no need for separation of the Schweninger-Buzzi type of macular atrophy from the other forms of primary anetoderma. As in the diffuse idiopathic atrophy or acrodermatitis of Herxheimer, an inflammatory stage precedes the primary macular atrophy. This is part of the disease process, while in the secondary macular atrophy the inflammation is due to the antecedent disease.

DR. ANTHONY C. CIPOLLARO: In my experience, the changes of lupus erythematosus, whether of the discoid or the seborrhea congestiva type, together with macular atrophy, whether of the Jadassohn or the Schweninger-Buzzi type, were unusual, and for that reason I presented the case. Dr. Brown's search of the literature showed that Little reported a case of the combination of lupus erythematosus with macular atrophy, and Pringle, in discussing Little's case, bore out the fact that there is such an association. Does the lupus erythematosus have anything to do with the macular atrophy, or are the two diseases different? Dr. H. E. Michelson, of Minneapolis, thought the lesions on the face of this patient might be those of sarcoid, which not infrequently ends with macular atrophy, and I think that was an interesting observation. We could not find evidence of sarcoid, whereas we have evidence of macular atrophy and lupus erythematosus. We were not able to determine in this case whether macular atrophy follows lupus erythematosus or whether they begin independently of each other.

Case for Diagnosis: Angioblastoma of Groin: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi? Presented by DR. ANTHONY C. CIPOLLARO.

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Books

Color Atlas of Morphologic Hematology. By Geneva A. Doland. Price, $5.00. Pp. 74. Harvard University Press, Cambridge, Mass., 1951.

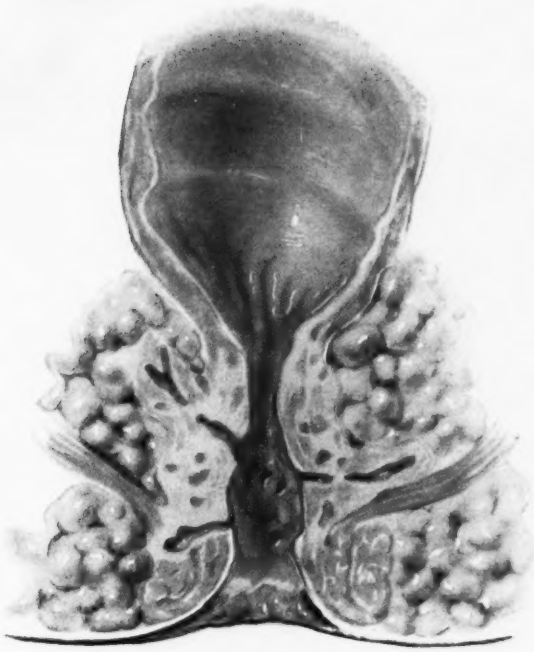
This small, concise volume, written by the chief laboratory technician in hematology at the Thorndike Memorial Laboratory of Boston City Hospital, and edited by Dr. Thomas Hale Ham, Professor of Medicine, Western Reserve University School of Medicine, has been published as a companion book to "A Syllabus of Laboratory Examinations in Clinical Diagnosis," a comprehensive text also edited by Dr. Ham. The Atlas is intended as a guide for reference in the study of films of peripheral blood stained with Wright's stain. It contains 14 plates in color by Etta Piotti, 2 of which depict normal and abnormal cells of the erythrocyte and leucocyte series, and 12 of which are illustrative of blood pictures encountered in various pathologic conditions. Nine diagrammatic plates, containing drawings in black and white, are devoted, in the main, to the maturation of the various strains of blood cells. One plate (Fig. 8), showing histiocytes in the peripheral blood in selected clinical cases, is portrayed in drawings of black and white. This may have been done for the sake of economy in production, but the value of the book would have been enhanced if this plate had been reproduced in color.

A valuable feature of the Atlas is the presentation of clinical and hematologic data, and the author's interpretation, concerning each disorder portrayed in the colored plates. In the opinion of this reviewer, this feature should prove invaluable to the medical student, the practitioner, or the clinician who has not become a specialist in the field. The value of an atlas in the field of hematology, no matter how excellent the text, lies primarily in the faithfulness and excellence of the reproduction of blood cells in color. On the whole, the reproductions in this volume are unusually good, although in certain instances some of the finer details of nuclear structure are not very well shown (for example, in the proerythroblast, Plate I, and in the lymphoblasts and young lymphocytes, Plate XII).

According to a note in the foreword, consideration of the morphology of cells of the bone marrow has been omitted intentionally, since cells of the marrow may be seen in the peripheral blood in certain physiologic or pathologic conditions. While this statement in general is true, study of preparations of aspirated marrow material often yields information that cannot be obtained solely from examination of films of the peripheral blood (in the presence of such diseases as metastatic carcinoma, Gaucher's disease, Niemann-Pick disease, and others). The addition of one or more colored plates showing abnormal types of cells found in the bone marrow, and their differentiation from osteoclasts and osteoblasts, would have added significantly to the value of the book. One also wishes that a plate in color of megaloblasts in various stages of development had been included. These cells are described on page 6, but are not illustrated. They may be seen rarely in films of peripheral blood in patients who have pernicious anemia in severe relapse.

The hematologic terminology employed throughout the text is lucid and is in fairly close agreement with the terminology used by most hematologists in recent years. With the exception of the terms used for the erythrocytic series, and the use of the adjective "young" instead of the prefix "pro" for intermediate cells of the leucocytic series, the author has followed the definitions proposed three years ago by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs.

This book can be recommended unreservedly as a valuable addition to the hematologic literature, and it should prove very useful, together with the Syllabus, in physicians' offices, hospitals, or clinical laboratories.



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Wright, L. T., et al.: Antibiotics and Chemotherapy 1:193 (June) 1951.

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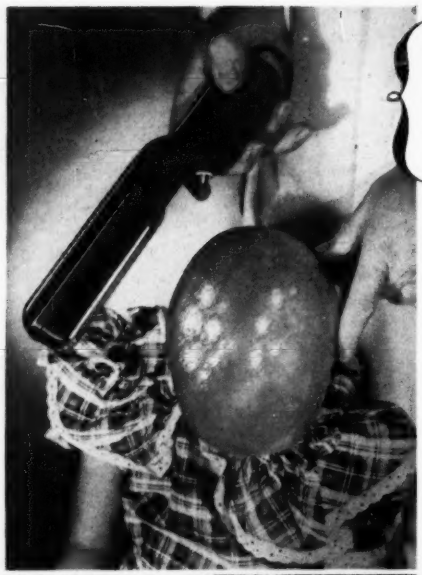

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3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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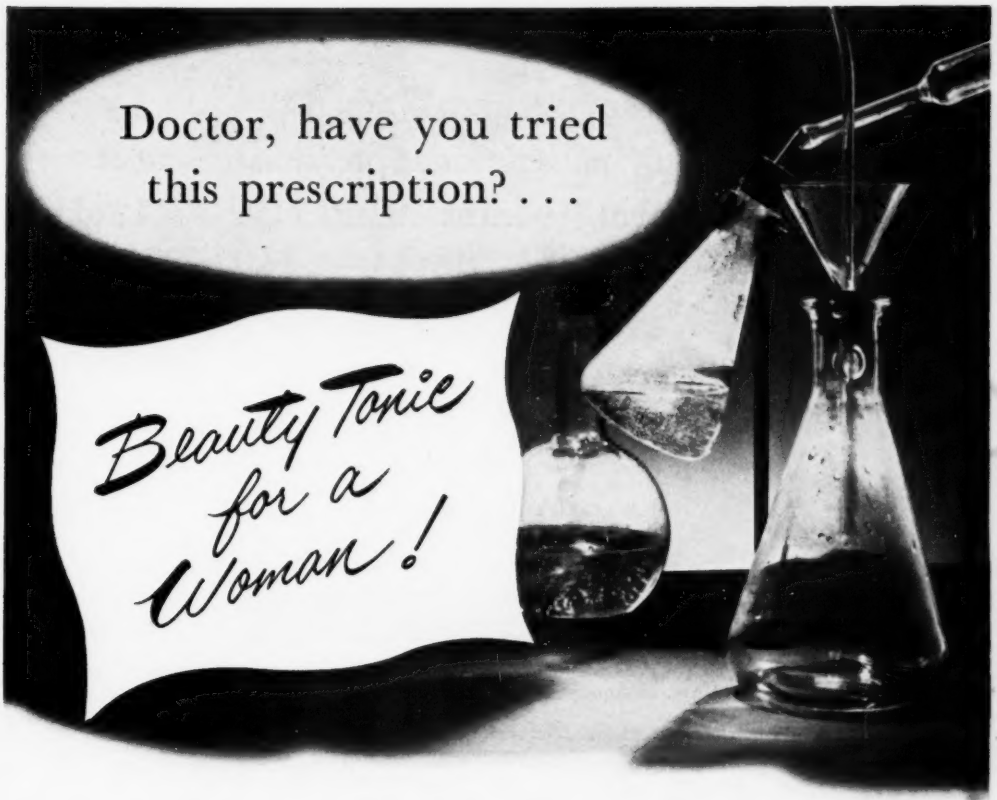

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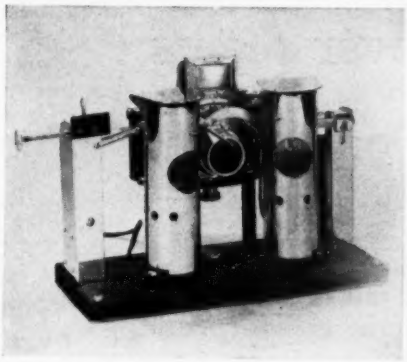

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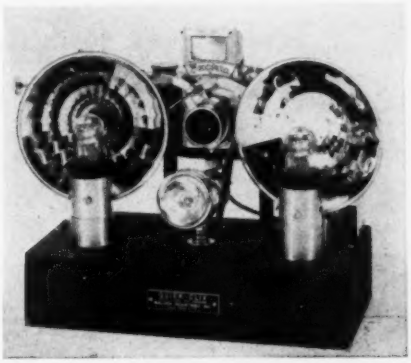

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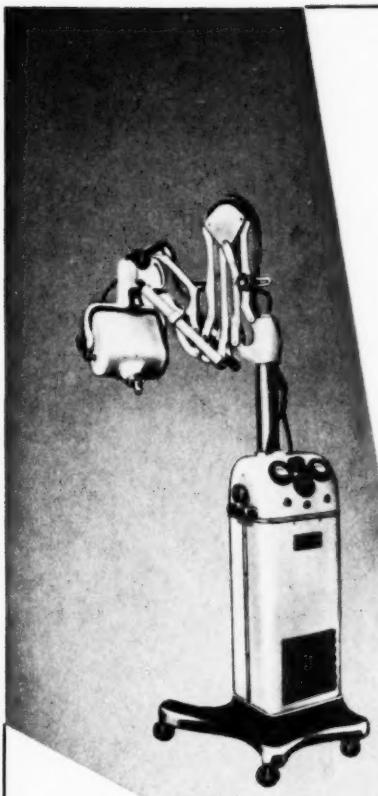

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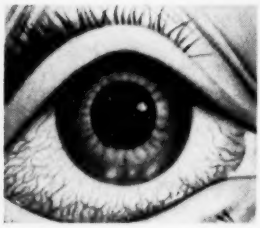
Cortone®

Ophthalmic Dosage Forms Provide Dramatic Benefit in Inflammatory Eye Disease

SUPERFICIAL KERATITIS



Pretreatment

After 3 days' treatment

CORTONE instilled topically every ½ hour during the day and every two hours at night.

Topical Therapy Proves Effective, Convenient, and Economical

In a recent study,[1] CORTONE applied topically, afforded best results in the treatment of lesions of the anterior segment where the response, at times, was phenomenal. The authors recommended that CORTONE be administered locally, when feasible, because of the simplicity of the method, lack of irritation, and absence of undesirable physiological side effects. Other workers[2] noted, "Local therapy . . . reduces the cost to the individual patient . . ."

1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* **45**:301, March 1951.
2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* **34**:361, March 1951.

Literature on request

Cortone®
ACETATE
(CORTISONE Acetate Merck)

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